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American Heart Journal

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Original Communications

EFFECTS OF PHYSICAL STRAIN AND HIGH ALTITUDES ON THE HEART AND CIRCULATION

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IT IS with some hesitation that I address this group of experts on cardiac function on such a subject as that assigned to me. I am not a physician nor can I speak authoritatively about one of your principal tools, the electrocardiograph. Despite these limitations I am encouraged to come before you by two facts. First, despite the rapid advances in cardiology in recent years, there remain wide gaps in our knowledge of cardiac function in healthy human beings. One of these has been narrowed by my good friend Ashton Graybiel at this meeting; he has discovered unexpectedly large variations in the electrocardiograms of several hundred healthy students and flying cadets. Second, working with many associates in the Harvard Fatigue Laboratory, and, in recent months, in the Aero Medical Research Unit at Wright Field, I have learned much about the cardiovascular response to exercise and to high altitudes. I propose to discuss some recent observations regarding the dependence of cardiovascular responses to moderate and severe exercise on age, training, race, and environmental conditions.

The measures of cardiovascular function which were used include the heart rate, the total oxygen uptake, a derived function, the "oxygen pulse," and the cardiac output. The total oxygen intake during maximal work is perhaps the best functional test of cardiorespiratory performance. It depends upon the volume of air supplied to the lungs, on conditions controlling diffusion in the lungs, on the rate of blood flow, and on the oxygen content and carrying capacity of venous blood. The "oxygen pulse" is derived from the first two functions; it amounts to the oxygen delivered to the tissues per beat of the heart. The cardiac

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output in man is best measured by the acetylene method of Grollman.[1] In the dog it may be estimated directly by puncture of an artery and of the right side of the heart, and ascertaining the oxygen content of each sample and also the oxygen consumption of the animal. Unfortunately, neither of these methods is satisfactory during maximal exercise.

Cardiovascular responses to moderate exercise have a notable dependence on age. We have studied the performance of a large number of subjects doing a fixed task on the treadmill, i.e., walking at 5.6 km. per hour up a grade of 8.6 per cent. This can be accomplished by boys of 6 years or men of 70. The oxygen consumption is about seven times the basal rate. The heart rate after fifteen minutes of such work is much higher in boys than in men of middle age. Robinson,[2] working in the Fatigue Laboratory at Harvard, has shown that such work produces a mean heart rate of 170 in 6-year-old boys, as contrasted with 134 in men of 42 (Table I).

TABLE I

HEART RATES DURING GRADE WALKING

(The speed was 5.6 km. per hour, and the grade, 8.6 per cent. This raises the oxygen consumption to about seven times basal.)

AGE (YEARS)	HEART RATE
6	170
10	164
14	160
18	150
22	146
26	143
30	140
34	137
38	134
42	134

Young dogs have high heart rates; these appear to reflect great sympathetic stimulation. It has been shown by Brouha and his associates[3] that, after the dog has been sympathectomized, his performance during moderate exercise may remain unaffected, in so far as fatigue, accumulation of lactic acid, and mobilization of energy reserves are concerned, and yet a given task will be accomplished with a much slower heart rate, and, therefore, with a much larger oxygen pulse. It appears that before the operation the heart rate is unnecessarily high. These facts suggest that the high heart rates among boys reflect the prodigality of youth as contrasted with the conservatism of age; it is well established that youth excels in bursts of intense activity, but that the older man may be superior in sustained activity of more modest intensity.

Measurements of oxygen consumption during moderate activity show no great variation in over-all mechanical efficiency with age, but, since the heart rate is slower in the older man, it follows that his "oxygen pulse," or the oxygen delivered per beat, is greater than in the young man. The measurements of cardiac output during moderate work do

not show any striking variation between the ages of 20 and 50. Data on this subject are inadequate and need amplification. All of these facts indicate that, although the mechanical efficiency of the body as a whole does not vary much with age, cardiac efficiency may be greater in the older man provided he is in good health. It should be emphasized that we have been discussing efficiency in the true engineering sense, i.e., the ratio of output of useful energy to total energy input. We shall now direct our attention to the *capacity for work*.

The capacity for work of the body as a whole may be measured in a variety of ways. An index to the capacity for anaerobic work is gained by timing a man in a quarter-mile race. An index to his capacity for aerobic work is given by his performance in a marathon race. Corresponding practical tests in military circles would consist in ascertaining how many yards a soldier, carrying his equipment, can cover in one minute, and how many miles per day he can march. Other practical tests are given daily in the wheat field, in the lumber camp, in the steel mill, on the battleship, and in the tank.

TABLE II

MAXIMAL ATTAINABLE OXYGEN INTAKE OF THE AUTHOR FROM THE AGES OF 37 TO 50

YEAR	MAXIMAL OXYGEN INTAKE (L. PER MIN.)
1928	3.28
1930	3.26
1931	3.35
1933	3.23
1935	3.26
1936	3.17
1937	2.90
1939	2.98
1941	2.87

Quantitative measurements can be made in the laboratory. They reveal that man's best performance during intense activity is attained between the ages of 18 and 25. His maximum heart rate then lies between 190 and 210, and he can reach higher levels of oxygen consumption during this time than ever again. Thereafter, his decline can be traced. He may be able to use 4 liters of oxygen per minute at the age of 20, and only 3 liters per minute at the age of 50. At the same time, the maximum heart rate he can attain during exercise falls off; it is likely to lie between 160 and 170 at the age of 50, and may not exceed 150 at the age of 70. These observations were made by Robinson,[2] chiefly on a group of nearly 100 men and boys, all of whom were in good health. Although most of these subjects were studied only once, the results are in harmony with observations made on some of ourselves during the past 10 to 15 years. In my own case, for example, my maximum heart rate has declined from about 172 to 162 per minute, and my maximum oxygen consumption from about 3.3 to 2.9 liters per minute, since 1928, as shown in Table II.

Unfortunately, we have no reliable method of measuring cardiac output during maximal activity. There can be no question that, as the capacity for oxygen supply falls off, the capacity for pumping blood declines also, but we do not know how closely this decline parallels the decline in oxygen consumption. The best evidence indicates that it is the young man who is able to utilize the most oxygen as blood passes through the capillaries. He accumulates the highest concentrations of lactic acid in his blood, as shown by Robinson and Harmon;[4] the greater acidity thus produced favors the unloading of oxygen in his tissues. The well-trained young man can accumulate twice as much lactic acid as the untrained man and is able to transform more energy anaerobically on this account.

During the summer of 1939, ten of us from the Fatigue Laboratory set up a temporary laboratory in the high school at Benoit, Mississippi, in order to study the work capacity of young sharecroppers, both white and colored, and to ascertain the effects on our own party of this hot, humid climate.[5] Particular attention was paid to cardiovascular functions. Attempts were made to carry on for two hours enough work to increase the basal oxygen consumption sevenfold. The handicap imposed by temperatures of 85° to 90° F. and a humidity of 80 per cent soon became evident. Sweating began, and soon reached a rate of 1 to 2 liters per hour. Body fluids were thus depleted, and, at a time when the blood volume was decreasing, there was an increased opening of peripheral vessels. The body temperature of the less fit persons (including most of the Northerners) was rising steadily, and their efficiency was steadily becoming less. At the same time the pulse rate was increasing; the cardiac output was declining; and the systolic blood pressure was falling. Some members of our party were unable to continue for more than an hour, and the best of us were nearly exhausted after two hours.

All of the sharecroppers were able to complete the two hours. The white sharecroppers gave a much better performance than our group. They were more fit, and they had the great advantage of being leaner. The negro sharecroppers were much superior to the white sharecroppers. Most of them reached a state of equilibrium with a rectal temperature of about 101° F. and a pulse rate of 150, as compared with 102° F. and 170, respectively, for the whites. They sweated less and drank more, and they had a higher over-all efficiency. We do not fully understand this superiority of the colored men, but believe it depends on a number of factors, rather than on a single factor. Their high efficiency, their lack of surplus fat, and their excellent physical condition contributed to their success in carrying out this severe test, but it is a fair assumption that the superiority of their cardiovascular function was a major factor.

It goes without saying that the two groups of sharecroppers overlapped in their rating on this test. Of twenty-three negroes, two or three

were below the average performance of the whites. Of the seven whites, one was better than the average negro. One of the poorest performances was given by a negro house servant who was later found to have active and untreated syphilis. Additional details are shown in Table III.

TABLE III

WORK PERFORMANCE OF COLORED AND OF WHITE SHARECROPPERS AT A TEMPERATURE OF ABOUT 30° C. AND A RELATIVE HUMIDITY OF 80 PER CENT

	COLORED SHARECROPPERS	WHITE SHARECROPPERS
Number	20	7
Duration of work (min.)	120	120
Final rectal temperature (° C.)	38.26	38.64
Final skin temperature (° C.)	33.95	34.49
Final mechanical efficiency (%)	25.6	27.5
Final blood lactate (mg. %)	27.0	22.3
Final blood sugar (mg. %)	104	114
Final R. Q.	0.86	0.85
Final heart rate	152	173

These studies support the opinion often expressed by plantation owners that negroes are more resistant than whites to the ill effects of humid heat. It is commonly said that negroes can outwork their mules in plowing cotton. Although it is admitted that our observations are too few to be of great significance, it appears that a comparison of the performance of white and colored troops in the wet tropics might well be carried out in order to test adequately the military importance of these studies.

The same subjects were also tested in a run to exhaustion which lasted not more than five minutes. High temperatures and high humidity may aid, rather than hinder, performance in a test of such short duration. Our principal aim was to compare the performance of sharecroppers with that of northern college students. The former did as well, if not better, in most respects. They attained as high a heart rate; they ran about as long; and their maximal oxygen intake, per unit of body weight, was nearly the same. Of the two groups of sharecroppers, the negroes were somewhat superior to the whites. It may be concluded from these observations that, in such a rich farming country as the Mississippi Delta, conditions permit the development of high physical fitness. We must bear in mind, however, that the high infant mortality among negroes may eliminate the less fit, and that those who were examined were probably more highly selected than the college students, in so far as native physical endowment is concerned.

The heart rate attained during submaximal exercise is remarkably uniform for a given person under given environmental conditions. Some years ago Professor L. J. Henderson prepared two families of curves representing my heart rate and that of Frank Consolazio, my assistant. The external temperature was kept constant in a given experiment, and the heart rate was recorded after ten minutes of graded work on the

bicycle ergometer. The temperature varied from 0° to 50° C., and the oxygen requirement, from 0.6 to 2.6 liters per minute. The humidity at the higher temperatures was kept at about 50 per cent, and the air movement was minimal. The families of curves shown in Figs. 1 and 2 were extraordinarily reliable; the probable error within the range shown was not greater than two or three beats per minute.

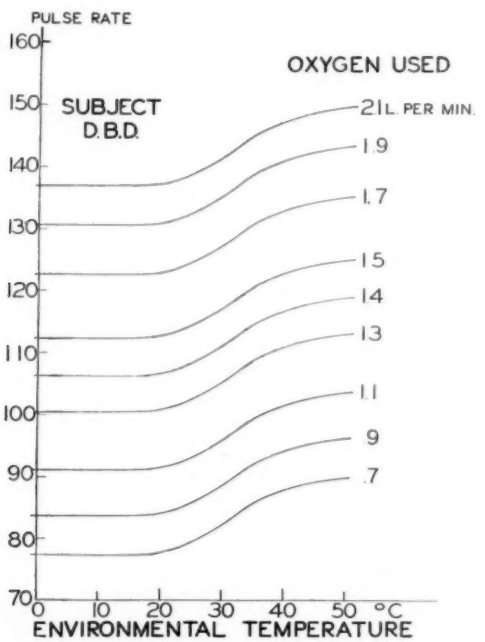

Fig. 1.—Pulse rate of the author as a function of external temperature and grade of work. In the higher temperatures the humidity was about 50 per cent and air movement was minimal. The pulse rate was observed in every instance after ten minutes of work. The mean deviation of the pulse rates from the curves did not exceed two or three beats per minute.

We have been considering, until now, cardiovascular responses to exercise and to the added complication of high temperatures. Turning to another environment, high altitudes, stresses of another sort are presented, namely, inadequacy of oxygen supply with, not infrequently, the hazard of cold. For the aviator there are many additional hazards, of which only one will be mentioned here, i.e., aeroembolism. To simplify the discussion, attention will be directed first to the man who is fully or partially acclimatized to high altitudes, and then to the aviator who has had no opportunity for acclimatization and only a short time for adaptation.

The most extraordinary high altitude communities are on the sides of volcanoes in nothern Chile. About 100 men, with some women and children, live on Mt. Aucanquilcha at 17,500 ft. Each morning the men climb up a zigzag trail to the mine, at 18,500 to 18,800 ft. There

they spend the day mining sulphur with pick and shovel, and loading it into the buckets of an aerial cable-way. When the day's work is over, they return to camp, where they eat, sleep, and play. Each of these communities has its soccer team, and these were often seen in practice, looking ahead to a Sunday's game at Ollagüe, a mile lower.

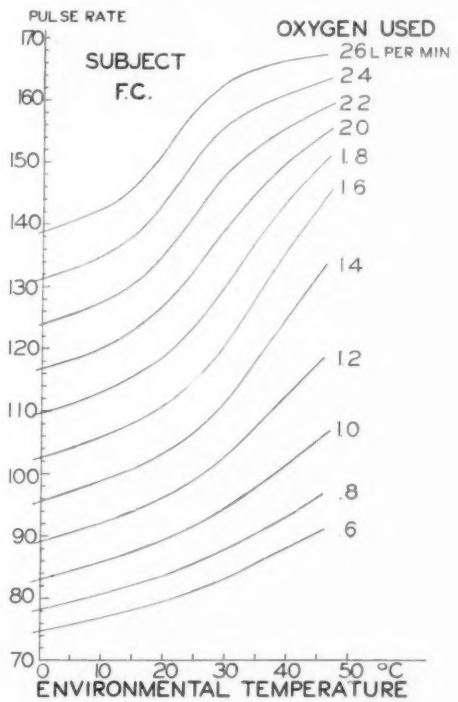

Fig. 2.—Pulse rate of subject F. C.

Our studies of ourselves at altitudes ranging up to 20,000 ft., and of Aucanquilcha workmen,[6] revealed the mechanisms of acclimatization which enable man not only to survive, but to carry on a fairly comfortable life at such an altitude. The resting heart rates of the men at Aucanquilcha were low—usually between 55 and 70. Their blood pressure was within the usual limits. The most striking change was in the physicochemical properties of the blood. The alkaline reserve was reduced by more than a third, and the hemoglobin was increased 50 per cent. Associated with this increase in hemoglobin there were corresponding increases in erythrocyte counts and hematocrit readings. The blood was so thick that it was difficult to draw it through a 20 gauge needle.

What do these changes imply with regard to the supply of oxygen and the work of the heart? The arterial blood was found to be about 75 per cent saturated. It contained, therefore, 0.75×30, or about 22.5 volumes per cent of oxygen, which is approximately one-sixth more than

is contained in the blood of a normal man at sea level. For rest and exercise, which cause a doubling of oxygen utilization, the calculated oxygen tensions are shown in Table IV. These values are in part hypothetical, but are probably not far wrong. They indicate that the partial pressure of oxygen in venous blood, and hence in tissues, can be kept remarkably high after man has become acclimatized to this altitude. This is possible because of the high level of hemoglobin available for oxygen transport.

TABLE IV

OXYGEN TRANSPORT AT SEA LEVEL AND AT HIGH ALTITUDES

	OXYGEN UTILIZATION (C.C. PER LITER)	ARTERIAL PO_2 (MM. HG)	VENOUS PO_2 (MM. HG)
A. Normal Man at Sea Level			
Rest	60	88	37
Work	120	88	22
B. Acclimatized Man at 17,500 Ft.			
Rest	60	42	30
Work	120	42	22

The dusky appearance of these men was somewhat like that seen in polycythemia vera; it depends on congestion of capillaries with thickened blood. The circulatory handicap caused by the increased proportion of erythrocytes is considerable, but is not as great as might at first appear. The work of Fåhraeus and Lindquist[7] indicates that in vessels of the size of arterioles the blood flows in a nonturbulent fashion, i.e., the cells move in an axial stream without much contact with one another or with the vessel walls. The resistance is chiefly caused by contact of the arteriolar walls with the more slowly moving plasma. Since the plasma of the acclimatized man is no more viscous than that of a man at sea level, it follows that the work done in circulating the blood is not greatly increased because of an increased proportion of erythrocytes.

None of our own party attained as complete acclimatization as the residents. Our hemoglobin increased only 25 per cent, and, although we spent from one to three weeks at 17,500 ft., we never became comfortable there. Our work capacity was greatly reduced. The most surprising observation was that the maximum heart rate that could be attained with exercise was less the greater the altitude. Neither could much of an oxygen debt be accumulated. The increase in blood lactic acid after strenuous exercise was less than half normal at 17,500 ft. One day Edwards and I climbed to 20,000 ft., finishing with a final burst of speed, relatively speaking. We at once drew blood from one another; subsequent analyses showed that the lactic acid content was hardly above the usual rest level. Another phenomenon, which is familiar to all climbers in high altitudes, is worth emphasizing, namely, shortness of breath on exertion. This shortness of breath makes climbing a very slow and

usually an intermittent process. One takes a few steps upward and stops to rest. One minute's rest is enough, and this makes it clear, considered in conjunction with the small increases in lactic acid, that the controlling factor is gas exchange, not accumulated, unoxidized end products.

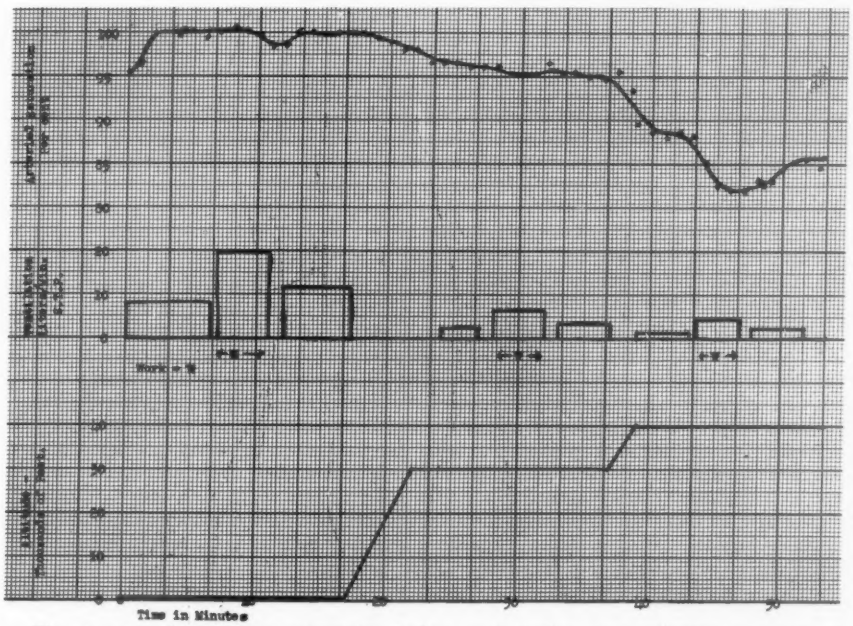

Fig. 3.—Arterial oxygen saturation before and during four minutes of work at 40,000 ft. The subject breathed pure oxygen and attained an oxygen consumption of about 1.5 liters per minute.

Recent studies in the pressure chamber at Wright Field threw light on this phenomenon. With rest or easy work, the conditions shown in Table IV obtained; the arterial pO_2 can be kept up by increased pulmonary ventilation. With such heavy work as climbing, however, the arterial pO_2 drops, the increased anoxia stimulates respiration to a hyperpneic level, and, even so, the oxygen content of arterial blood falls off. Fig. 3 illustrates the fall in arterial pO_2 when hard work is attempted at 40,000 ft., breathing pure oxygen, and the rapidity of recovery. The phenomenon depends on overtaxing of the diffusion capacity of the lungs; although a gradient of 1 or 2 mm. Hg is enough to supply the resting oxygen requirement, this proves wholly inadequate for heavy work.

An additional point of undoubted importance is the effect of the more alkaline state of the blood (produced by hyperventilation, unaccompanied by much lactic acid formation) on the unloading of oxygen. Although this favors the uptake of oxygen in the lungs, it hinders the release of oxygen in the tissues.

This picture, it seems to me, resembles that which is seen in the old man with a healthy cardiovascular system, but with the limitations to which all persons of advanced years are subject. He, too, has a low maximal heart rate; he is unable to accumulate much lactic acid during exercise; he has a reduced capacity for supplying oxygen to his tissues; and he experiences shortness of breath on exertion.

We come now to the stress and strain experienced by the aviator, in so far as they concern his heart and circulation. No acclimatization can be expected in his case because he spends, at most, only a few hours daily at high altitudes. His adaptive responses must be immediate; they are respiratory and circulatory.

Recent measurements of Asmussen and Chiodi, et al.,[8, 9] throw new light on the mechanisms of immediate respiratory and circulatory responses to acute oxygen lack. Their work amounts to an extension to intact man of the hypotheses advanced by Heymans[10] and Schmidt[11] and their associates regarding the role of the carotid body in respiratory and circulatory regulation.

Asmussen and Chiodi produced oxygen lack in some instances by moderate carbon monoxide poisoning, and, in others, by means of an air-nitrogen mixture. In each case there was a reduction of 20 to 30 per cent in the oxyhemoglobin of the arterial blood. Physicochemically, the effects on the blood are quite different. The dissociation curve of the available hemoglobin is displaced to the left by carbon monoxide poisoning. In this state the oxygen saturation of the available hemoglobin and the *arterial* pO_2 will be normal, but, for a given oxygen utilization, the *venous* pO_2 will be greatly reduced. In the low oxygen experiments—hypoxic hypoxemia—the oxygen dissociation curve is unchanged. The oxygen saturation of the available hemoglobin and the pO_2 of arterial blood will be reduced. If the oxygen utilization is unchanged, the venous pO_2 will be reduced, but to a less extent than in carbon monoxide hypoxemia.

The physiologic effects of these two forms of hypoxemia on the circulation and respiration were measured during rest and two grades of exercise. In summary, the results are shown in Table V.

The respiratory measurements show little increase in the volume of air breathed in carbon monoxide poisoning until work becomes heavy, but very considerable effects when a low oxygen mixture is breathed. It is presumed that in the former state there is no oxygen lack in the carotid body, whereas in the latter state there is a considerable oxygen lack there. This explanation can be maintained if we assume that the oxygen consumption of the carotid body is low in relation to the arterial supply, which we know is abundant, so that the reductions in combined oxygen, and hence in pO_2, are small. This means that in carbon monoxide poisoning the pO_2 in the carotid body is not much below its usual value. When the pO_2 of the arterial blood which is supplied to the

carotid body is low—as at high altitudes, or when a low oxygen mixture is breathed—the pO_2 within the carotid body will be even lower, and a strong stimulus is transmitted to the respiratory center. An early result of this hyperventilation is to produce an alkalosis which would normally inhibit respiration. A balance must be struck between their opposing forces; evidence of this conflict is seen in Cheyne-Stokes breathing.

TABLE V

A COMPARISON OF TWO FORMS OF HYPOXEMIA

	REST	LIGHT WORK	HEAVY WORK
Relative Respiratory Volumes			
Normal	100	450	750
CO-hypoxemia	100	440	950
Anoxic hypoxemia	160	650	1,360
Average Pulse Rates			
Normal	59	102	135
CO-hypoxemia	67	137	173
Anoxic hypoxemia	74	141	172
Average Cardiac Outputs (l. Per Min.)			
Normal	4.7	11.4	15.5
CO-hypoxemia	5.1	12.8	16.4
Anoxic hypoxemia	8.8	18.7	24.1
Average Stroke Volumes (c.c.)			
Normal	80	112	117
CO-hypoxemia	76	104	105
Anoxic hypoxemia	118	136	143

The circulatory responses are somewhat more complicated than the respiratory, for we observe increased pulse rates with an unchanged cardiac output in carbon monoxide poisoning, whereas both are increased in hypoxic hypoxemia. The increased pulse rate in carbon monoxide poisoning may be looked upon as a pressoregulatory compensation for the vasodilation. A stimulation of the circulatory center, in an attempt to compensate for the low pO_2 in the tissues, apparently does not take place. Asmussen and Chiodi conclude from their experiments that acute oxygen lack in tissues is neither directly nor indirectly a stimulus for the circulatory center.

On the other hand, it is obvious that in hypoxic hypoxemia, in which the arterial pO_2 is low, there is stimulation of the mechanisms which regulate the circulation. In this connection, Schmidt and Comroe[11] have shown that a low arterial pO_2 increases pulse rate and blood pressure if the chemoreceptors of the carotid body are intact, but not if they are denervated. It seems reasonable to conclude that the chemoreceptors of the carotid and aortic bodies originate the stimuli that result in the increased cardiac output when the arterial pO_2 is low.

The aviator of today, unless he is foolhardy, does not venture above 15,000 ft. without his oxygen supply, and he does not remain long above

12,000 ft. without oxygen. If he ventures as high as 20,000 ft. without oxygen, he is in danger of collapse. Let us assume, therefore, that he is a pilot in the Army Air Corps, and is provided with the most recent type of oxygen equipment. Our equipment, which was developed by Dr. Boothby, Dr. Lovelace, and Dr. Bulbulian, at the Mayo Clinic, in cooperation with experts in the Materiel Division of the Army Air Corps, is recognized as having limitations, but it has proved both economical and practical in most situations so far faced by Army pilots. With this equipment the pilot can climb to 30,000 ft. without serious oxygen lack. At 40,000 ft. the atmospheric pressure is one-fifth normal, and, even if he is supplied with pure oxygen, the blood does not take up its full quota. The reason for this is simple; the partial pressures of water vapor and of carbon dioxide in the lungs are about the same as at sea level. At sea level their effect is to displace air, but at 40,000 ft. they displace oxygen. Their diluting effect is about five times as great when one is breathing oxygen at 40,000 ft. as when breathing air at sea level. This is illustrated in Table VI.

TABLE VI

THE DILUTING EFFECTS OF WATER VAPOR AND CARBON DIOXIDE

	BREATHING AIR AT SEA LEVEL	BREATHING PURE OXYGEN	
		AT 30,000 FT.	AT 40,000 FT.
Total pressure (mm. Hg)	760	225	142
Alveolar pH_2O (mm. Hg)	47	47	47
Alveolar pCO_2 (mm. Hg)	40	40	38
Alveolar pO_2 (mm. Hg)	100	138	57
Alveolar pN_2 (mm. Hg)	573	0	0

There are hazards other than oxygen lack to contend with, not the least important of which is cold. Major Armstrong has discussed, in his book on aviation medicine,[12] the handicap imposed by cold. He estimates that, at a cockpit temperature of 0°F., there is a 30 per cent loss in efficiency in performing necessary tasks, and that the loss may reach 80 or 90 per cent at –30° to –40° F. This ineffectiveness is caused by frosted goggles and windshield, cold hands and feet, and the clumsiness associated with wearing bulky clothing.

There is some interdependence of the effects of cold and of anoxia. Inadequate oxygenation of the blood results in a lowered oxygen tension and dilatation of capillaries in active tissues. The increased capillary bed leads to a diversion of blood from less active areas. This slower movement of blood through the extremities contributes to their chilling. Hence an adequate oxygen supply is particularly important if the cockpit is ineffectively heated.

Although pilots are not likely to experience frostbites, members of the crew are commonly exposed to lower temperatures, both of the air in their compartments and of the metal around them. If the oxygen supply

fails and its user faints, his hands and face may come in contact with cold metal so that serious frostbites may result. In caring for such a man, other members of the crew should remember the hazards of cold as well as the hazard of anoxia. Such a man should continue to receive pure oxygen for some time after returning to the ground. The extra oxygen thus supplied favors recovery of injured tissues.

Aeroembolism has been discussed at some length by Armstrong.[12] It may be experienced at 30,000 ft., and is very likely to occur after some time at 40,000 ft. It takes various forms but always may be attributed to the formation of gas bubbles in tissues or body fluids. The formation of these bubbles has a simple physical explanation—a sudden reduction in pressure to one-fifth atmospheric produces a supersaturated solution of nitrogen; four-fifths of this nitrogen is in an unstable state. Much of it is eliminated by the lungs, but some bubbles form in the tissues. Once a bubble forms it may grow by accretion. Both carbon dioxide and oxygen diffuse into it, so that gas collected from emboli may contain no more than 50 per cent nitrogen.

The symptoms that may be caused by aeroembolism are as follows:

1. Bends.—Pains in the joints, particularly the knee and ankle. These usually disappear on descent, but, if they have been present for an hour or longer, they may persist in diminished intensity for some hours at ground level.

2. Itching.—This is technically known as formication and is a common symptom. It disappears during descent and leaves no after effects.

3. Second-degree Formication.—This may be considered an extension of *2*. Presumably, gas bubbles form in the skin and first become evident when they begin to press on nerve endings. These bubbles may impede the peripheral circulation enough to produce cyanosed areas, with perhaps some capillary damage, even though the arterial oxygen is undiminished. The itching stage gradually merges into pain, and the distress may become evident through perspiration, paleness, and other classical symptoms of shock. Most of the pain disappears at ground level, but the itching may persist for twenty-four hours, and red splotches on the skin, suggestive of those which are seen during recovery from severe carbon monoxide poisoning, may not disappear until two or three days have passed. This form of aeroembolism, in our experience, is most common in persons with too much subcutaneous fat. Possibly it is more likely to occur in the low-pressure chamber than in an airplane when the external temperature is low. Formication of the milder sort, however, is often experienced by pilots in high altitude flights.

4. Throat Irritation.—At first there is pain on taking a deep breath, and later a generalized irritation of the bronchial tree, accompanied by an unproductive cough. If the pain becomes continuous and more severe, dyspnea becomes evident and collapse may ensue unless one

descends rapidly to lower altitudes. Although this manifestation of aeroembolism is not usually the most distressing symptom, it is one of the most common, judging from our experiences during prolonged exposures to altitudes of 30,000 ft. and above. If the pains have been severe and prolonged, they may persist for some hours after descent.

5. Headache.—One of our subjects, after two hours at 30,000 ft., almost invariably develops a mild headache that does not disappear until several hours afterward. We have no proof as to the mechanism, but it may depend on bubbles in the cerebrospinal fluid.

Aeroembolism may be considered one of the most serious problems of the era of military aviation which we are now entering. The most serious aspect of aeroembolism is the prospect of circulatory collapse if the cumulative effects become intolerable. Unfortunately, there is at hand no wholly satisfactory remedy. Much can be done in the way of selecting resistant persons. The preliminary breathing of oxygen while exercising greatly increases one's tolerance, but this cannot be done practically in many situations.

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THE NORMAL HEART

Anatomy and Physiology of the Structural Units

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SIR ARTHUR KEITH,[1] in a Harveian lecture, quotes Harvey to the effect that "no physiological theory can be true unless it gives a complete and final explanation of all points of structure," and then inquires, "How far does our knowledge of the function of the mammalian heart fall short of explaining its structure?" That cardiac structure has been recurrently interesting and difficult to understand is attested by the following list of fifty-eight investigators, many of them prominent anatomists, who, during five centuries, have studied its morphology and have demonstrated repeatedly that the ventricles are made up of discrete muscle bands:

In the Sixteenth and Seventeenth Centuries.—Vesalius, 1514-1564; Stenson, 1630; Seger, 1661; Lower, 1669; Langelotte, 1675; Pechlinus, 1676; Bartholin, 1678; Borelli, 1681; Charleton, 1683; Morton, 1683.

In the Eighteenth Century.—Vieussens, 1706; Winslow, 1711; Keerwolf and Ruyschius, 1720; Morgagni, 1723; Santorinus, 1724; Lancisi, 1728; Forell, 1732; Stuart, 1738; Walther, 1738-1753; DeBlainville, 1740; Lieutand, 1740; Albinus, 1747; Senac, 1749; Haller, 1757; Wolff, 1780.

In the Nineteenth Century.—Wilson, 1859; Luschka, 1860; Lindes, 1865; Winckler, 1865; Sappey, 1869; Henle, 1876; Cruveilhier, 1877; Hesse, 1880; Allen, 1884; His, Sr., 1885-1886; Albrecht, 1887; Brown, 1888; MacAllister, 1889; Krehl, 1891; Haycraft, 1891; His, Jr., 1891; Thane, 1894; Kent, 1894; Seipp, 1895.

In the Twentieth Century.—MacCallum, 1900; Testut, 1901; Foster, 1901; Toldt, 1901; Knower, 1908; Luciani, 1911; Mall, 1911; Tandler, 1913; Shaner, 1924; Flett, 1927-1928; Robb and Robb, 1934-1941; Lowe, 1939-1941.

There is good agreement among all authors regarding the superficial muscles. Fig. 1, taken from Todaro,[2] shows the fibrous structures at the base of the heart from which the muscles take origin and upon which they again insert. The outer fibers, which arise from the conus tendon, the pulmonary root, the left trigonum fibrosum, and the anterior, lateral, and posterior curvature of the left auriculoventricular ring, were named superficial bulbospiral (SBS) by Mall,[3] in reference to the aortic bulbar (left) side of the heart. There is some variability in the extent of this origin; sometimes the fibers do not reach as far anteriorly and to the right as the conus tendon; sometimes they spread

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backward only to the midportion of the left posterior curve of the mitral orifice; or they may extend further over to the medial curvature of the posterior edge of the tricuspid orifice.

In contrast to the SBS, the outer fibers which arise around the tricuspid orifice were named superficial sinospiral (SSS) by Mall, in reference to the venous or right side of the heart. These two muscles extend spirally downward toward the apex; the superficial bulbospiral covers a considerable portion of the diaphragmatic surface of the heart, and the superficial sinospiral covers the most basal portion of the right ventricle posteriorly, much of the right ventricle anteriorly, and crosses in a narrower band to form the anterior horn of the left vortex. Together they cover the whole surface of both ventricles with a muscular layer only about 1 mm. thick, except at points around the base of the heart, where, through fenestrations, the deep sinospiral can be seen.

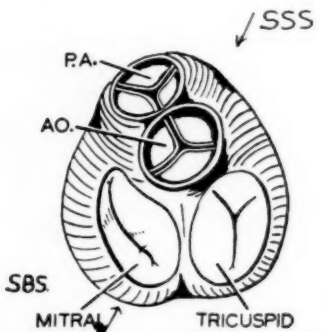

FIG. 439. The four orifices guarded by valves, showing the cusps (also the superficial muscle layer of the ventricle). (After Spalteholz.)

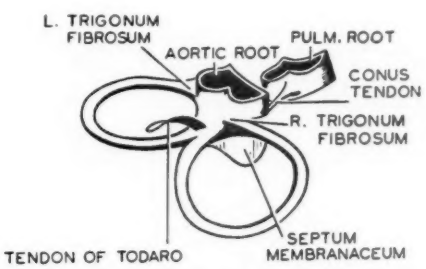

FIG. 440. The skeleton of the heart. (After Todaro.)

Fig. 1.—Copied from Grant: *A Method of Anatomy*, Williams & Wilkins Co., to show, in Fig. 440, the tendinous ring at the base of the heart from which the muscles take origin and to which they again insert. In Fig. 439 the superficial bulbospiral (*SBS*) arises from the conus (*P. A.*) and all around the mitral ring toward the left. The superficial sinospiral (*SSS*) arises around the tricuspid ring.

At the apex of each ventricle, but seen more easily on the left, the fibers form a vortex and penetrate to the interior of the ventricles, where they lie subendocardially and run spirally upward, surrounding both ventricular cavities, to attach to the tendons around the auriculoventricular orifices. This attachment may be either direct or indirect. Some fibers are pulled toward the interior of the ventricular cavities, and so form the papillary muscles, from which fibrous tendons (chordae tendineae) attach to the valve leaflets, and, through them, to the fibrous rings at the base of the heart. The superficial bulbospiral in the right ventricle, as well as in the left, forms a considerable portion of the inferior (posterior) papillary muscle, and attaches through the posterior leaflets of the mitral and tricuspid valves. On the right it

also gives many fibers to the anterior papillary muscle, whereas, on the left, relatively few pass to the anterior papillary muscle. The superficial sinospiral muscle contributes to the anterior and septal papillaries on the right side; it is attached both directly and indirectly, through the anterior and septal tricuspid leaflets, to the fibrous A-V ring. On the left this muscle also attaches directly, or, after forming the anterior papillary muscle, attaches by the chordae tendineae and the anterior mitral leaflet to the corresponding fibrous ring on the left.

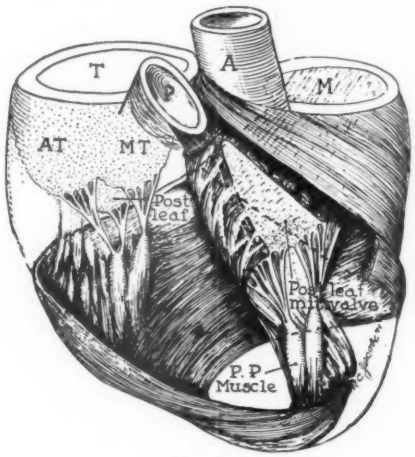

Fig. 2.

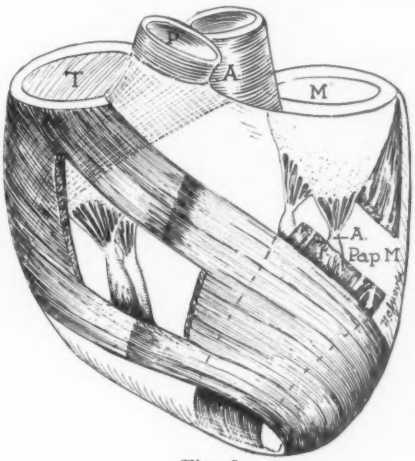

Fig. 3.

Fig. 2.—The superficial bulbospiral muscle as seen from the front of the heart (compare with Fig. 1, Robb, Hiss, and Robb,[7] which is a more schematic diagram of the same muscle, viewed from the diaphragmatic surface of the heart). *A*, Aorta; *M*, mitral orifice; *P*, pulmonary artery; *T*, tricuspid orifice; *AT*, anterior leaflet of tricuspid valve; *MT*, medial leaflet of tricuspid valve; *Post. leaf.*, inferior (posterior) leaflet of the tricuspid valve; *P.P.* inferior (posterior) leaflet of the mitral valve. A V-shaped section is cut from those fibers encircling the left ventricle subendocardially, so that the mitral valve may be seen. A similar band on the right is not sketched in because of technical difficulties.

Fig. 3.—The superior sinospiral muscle, as seen from the anterior surface of the heart (compare with Fig. 2, Robb, Hiss and Robb[7]). Symbols as in Fig. 2. Again the subendocardial layer has been cut through in order to show deeper structures. The window in the right ventricular wall shows the fibers from the trabeculated area running up to the anterior and medial leaflets of the tricuspid valve. In both of these superficial muscles, blood vessels follow the muscle strands as they encircle the apex, and either surround the ventricles or form the capillaries.

There has been more difficulty regarding definition of the deeper layers, but most authors are in essential agreement, as is shown by a comparison of the drawings by Mall,[3] Tandler,[4] Flett,[5] Shaner,[6] and Robb, et al. (Fig. 4.)[7]

The deep sinospiral muscle (DSS) (called part of the "middle layer" by Shaner,[6] and "Wandfassern" by Tandler[4]) encircles both ventricles, and lies deep to the previously described superficial layers. One portion arises at the anterior curve of the left A-V ring, and its fibers run more transversely than those of the superficial layer; other fibers enter from the whole circumference of this ring. At the posterior interventricular groove, this muscle splits; the deeper fibers enter the septum, whereas those which are less deep (along with those arising from the

right A-V ring) form the lateral wall of the right ventricle. The muscle is deficient toward both apices, for there are large oval apertures which are filled in by the superficial muscles (right and left vortices and papillary muscles) (Fig. 5).

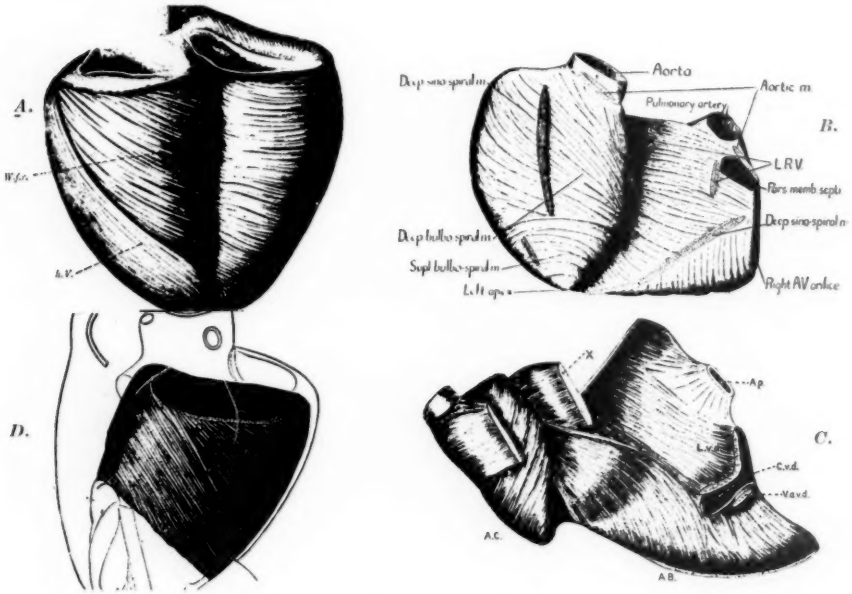

Fig. 4.—*A*, *B*, *C*, the deep spinospiral muscle, as described by three other authors. *A*. Fig. 81 of Tandler.[4] The dorsal surface of the heart is seen. The superior sinospiral and a little of the superficial bulbospiral muscles have been removed. The nearly transverse fibers of the deep sinospiral muscle are seen crossing the posterior interventricular sulcus. *h.V.*, Posterior "Vortexfasern"; (Mall's superficial bulbospiral muscle); *W.f.r.*, "Wandfassern" of the right ventricle. *B*, Fig. 6 of Flett,[5] to show the deep sinospiral muscle, also seen from the posterior surface. "Early stage of unrolling of the left ventricle. Aortic muscle and longitudinal muscle of the right ventricle severed." The basal portions of the superficial muscles have been removed. The deep sinospiral muscle has been cut at the posterior interventricular sulcus and the right ventricle pulled laterally. The deep sinospiral muscle fibers forming the medial wall of the right ventricle and part of the septum are well seen. *C*, Fig. 7 of Shaner[6]; a deep dissection of the fowl heart, posterior view. The deep sinospiral muscle, *AB*, has been cut at the posterior interventricular groove, and the ventricles still further separated. The course of the deep sinospiral muscle through the septum and its attachment on the front of the left ventricle are well seen. *A.B.*, Sinospiral muscle; *A.C.*, superficial bulbospiral muscle; *A.p.*, pulmonary artery; *C.v.d.*, cavity of right ventricle; *V.a.v.d.*, right A-V valve; *X*, deep bulbospiral muscle (cut to show subendocardial fibers of superficial bulbospiral muscle). This drawing is almost identical with Shaner's drawing of a like dissection in an adult pig heart, and with Mall's Fig. 8, showing the same structures and relations in a human heart. *D*, Mall's[3] Fig. 11, an anterior view of the deep bulbospiral muscle. The aorta with the two coronary outlets is seen, as is also the mitral orifice to the left.

The deep bulbospiral (DBS) is the only muscle which is confined to one ventricle. It is a strong circular cuff, and has both its origin and insertion in the medial (septal) curve of the mitral ring. The fibers form three interweaving bands which run circumferentially. This muscle surrounds both the mitral orifice and the aorta (Fig. 6).

The microscopic appearance of the heart is well known, but there is one aspect that deserves consideration. Because syncytial structure is present in the heart, it has been assumed that the whole heart is one syncytium. If this were absolutely true, the results of the labors of

the anatomists who have been cited would have to be considered as artifacts. If one views heart muscle sections which are cut in such a way that some areas are seen in cross section, well-marked septa are found to lie between the various fasciculi. Some of these septa are thicker than others, and, among the connective tissue strands, blood vessels, nerves, and Purkinje-like cells are found. Work is now in progress whereby, with the aid of Dr. Walter Greene, of the Department of Histology of Syracuse University, serial sections are being examined and reconstructions made to ascertain whether the muscle bundles are sheathed throughout their entire course by connective tissue.

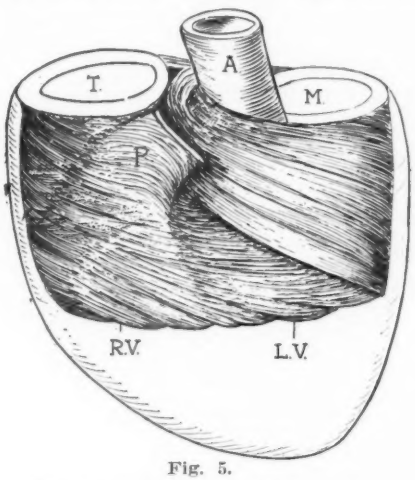

Fig. 5.

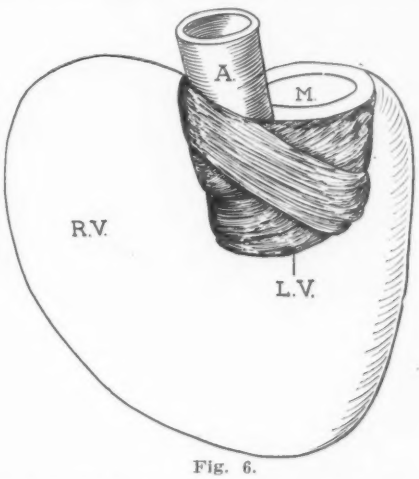

Fig. 6.

Fig. 5.—The deep sinospiral muscle as seen from the front. Note the division of the muscle at the posterior interventricular sulcus, with fibers passing anteriorly to form most of the basal two-thirds of the septum; these septal fibers lie just distal to the band of the left head of origin at the base of the aorta. Symbols as in Fig. 2. (Compare with Fig. 4, Robb, Hiss and Robb,[7] which is the same muscle sketched from the posterior view.)

Fig. 6.—The deep bulbospiral muscle, a powerful sphincter encircling the left ventricular base and enclosing both the aorta and the mitral orifice within its sweep. (Compare with Fig. 3, Robb, Hiss and Robb,[7] which is the same muscle seen from the posterior surface of the heart.)

The anatomists have been chiefly concerned in describing the course and attachments of these muscles, but a few have discussed function. In this laboratory, further study has been made of their (1) blood supply, (2) nerve supply, (3) electrical properties, and (4) function.

1. Blood Supply.—An adaptation of a Spalteholz-Banchi diagram indicating which coronary branches are distributed mainly to individual muscles has been published previously.[40] One should note that the coronary branches therein indicated are small. This information was first obtained by gross dissection and was later confirmed experimentally when such branches were tied. After an acute experiment the vessel peripheral to the ligature was injected with a dye, and dissections were made to confirm the localization. Still later, recovery experiments were performed, and the deposition of scar tissue was studied with reference to the muscle involved.

At the apices of the ventricles, where the superficial muscles penetrate to form the so-called papillary muscles, the more distal branches of the coronary tree (which have been bowed around in a series of arches concave toward the base of the heart) follow the muscle; they lie parallel to the muscle fibers, and run longitudinally from apex to base. These vessels supply the layer of muscle which lies nearest to the endocardium, thus making it unnecessary to postulate either direct nutrition from the ventricular cavity or a nutritive function of the Thebesian system (under normal conditions) to account for the fact that a thin layer of normal tissue lies adjacent to the endocardium when infarction has been produced by occlusion of a vessel which penetrates the thickness of the ventricular wall. This fact may prove to be very important in interpreting abnormal electrocardiograms and localizing lesions.

Our observations may be related to those of Schlesinger[9] that "coronary arteries in normal human hearts, even senile hearts, are true 'Cohnheim end arteries' without anastomotic connections; such anastomoses do not develop pari passu with increase in age." A conclusion of Blumgart, et al.,[10] is also pertinent: "In normal hearts intercoronary anastomoses larger than 40 micra in diameter are not found. Anastomotic communications measuring less than approximately 40 micra in diameter exist between the coronary arteries of normal hearts; their presence can be demonstrated by high pressure injections of watery solutions. These fine communications are probably of little functional significance in obviating the untoward effects of sudden coronary narrowing or occlusion." Karsner and Dwyer[11] had previously shown that coronary arteries are end arteries.

Lowe[12-15] has confirmed these observations by several unique methods. First, he dissected hearts from persons who were known to have had coronary attacks and found that the scar tissue followed muscle bundle distribution. Second, he investigated the heart from a patient who died of acute leucemia and found petechiae only along the blood supply to the superficial bulbospiral muscle. Third, he examined ruptured hearts and found that the pathway taken by the blood escaping through the wall was partly determined by the connective tissue sheaths between the muscle bundles along which dissection by pressure had occurred. Finally, he showed that "a gelatine mass can be injected into the vessels of a single ventricular muscle, provided a dynamic balance be maintained between the various branches of the system." Thus, our anatomic and experimental observations on dogs, namely, that coronary arteries are functionally end arteries and are limited in distribution to one muscle alone, have been confirmed in man. Lowe concludes: "The evidence that there is a series of separate muscle bundles in the ventricular wall of the mammalian heart, and that they function independently, is now very strong."

2. Nerve Supply.—The nerve supply of the mammalian ventricle has not been too well worked out by histologists. Sympathetic and parasympathetic fibers are distributed to the auricles and to the coronary arteries, but, to our knowledge, have not been traced to ventricular muscle. Glomset and Glomset[16] report that, in sheep, cattle, and hogs, large numbers of nerve strands enter the main bundle of His, form a conspicuous portion of its cross-section area, and also accompany smaller strands. They also write that "such nerve elements are found neither in the bundle nor in its subdivisions in man or dog."

The Purkinje system has been more thoroughly studied in ungulates than in the dog or man. Two main reasons for this are that in cattle the Purkinje cell retains its individuality, and does not mimic the histology of the heart muscle cell; also, in ungulates, this system is surrounded by a connective tissue sheath which can easily be injected with a colored substance; then, by dissection or corrosion, or by clearing methods, the myocardial distribution is readily followed, and can also be checked microscopically. This sheath is not continuous with the lymphatic system of the heart which was recently described by Drinker.[17] In ungulates the Purkinje system consists of a main bundle, right and left branches, a subendocardial network, and a myocardial network. The myocardial network has been described by Wahlin[18] and Abramson and Cardwell,[19, 20] among others. These papers may be consulted for critical analysis and bibliography. Mahaim[21] described a myocardial network along the right branch in the human heart. In the beef heart the main branches have been shown by Robb, Greene, and Robb[22] to be distributed to specific muscle bundles.

There has been a tendency for physiologists and cardiologists to assume that this system is distributed in the human heart in the same manner as in the beef heart. However, although Mahaim,[21] Tawara,[23] Mönckeberg,[24] Lewis,[25] and Yater[26] described an A-V node, Todd[27] and Glomset and Glomset[16] did not find a circumscribed node in the human heart to compare with that found in ungulates. Also, in the human heart, right and left branches were not found by Glomset and Glomset,[16] although they have been thought to be present by many others, especially by Mahaim,[21] Yater,[26] Wahlin,[18] and Oppenheimer, et al.[28, 29] Histologic reports on human heart sections taken from areas where one might expect to find Purkinje tissue do not agree, but range from one extreme, at which true Purkinje or "Purkinje-like" cells are described, to the other, at which these groups of fibers are said to be composed of ordinary myocardium. Possibly this disagreement results from personal equation, for Yater[26] stated that the bundle fibers resemble the ventricular fibers, but possess less myoplasm, and Mahaim[21] stated they can only be identified by following a given strand of tissue in serial sections.

There is also variance regarding the myocardial networks. Todd and van der Stricht,[27] who studied human hearts, found Purkinje cells ex-

tending "to the furthest extent of the ventricular myocardium." Glomset and Glomset[16] report that "cells which correspond to the description of Purkinje cells in man and the dog and to the drawings of these cells by Tawara[23] (Tafel V) are found under the endocardium in various parts of the ventricles. Such cells are often continuous with ordinary myocardial elements." Yater[26] stated: "Purkinje fibers in the substance of the human heart are impossible to recognize but doubtless exist, just as they do in the hearts of large animals." Oppenheimer (personal communication) stated that, although he found "Purkinje-like" cells in the human heart, he had never succeeded in serial sections in tracing the actual transition from these so-called Purkinje cells to ordinary myocardial cells. Todd[27] has stated his belief that all mammalian hearts have an essentially similar Purkinje system, but warned against the belief that no secondary pathways from auricle to ventricle exist (see Kent[30]). Todd[27] vigorously denied that there is an anatomic basis for the current conception of the origin and spread of the action current in the human heart. It is apparently a universal observation that, when Purkinje tissue has been traced to its final distribution, it becomes oriented in a plane parallel to the muscle fibers. This is true, of course, only for the most distally recognizable portion of a given pathway. Thus, in the bovine myocardium, the direction of terminal Purkinje fibers and muscles fibers is identical.

In conclusion, in the beef heart the existence of a bundle of His, right and left branches, a subendocardial Purkinje network, and a myocardial network with specific branches to the separate ventricular muscles is established, but whether a similar system, composed of either Purkinje, Purkinje-like, nerve, or even ordinary cardiac muscle cells, exists in the human heart is still being questioned.

3. Electrical Effects.—The discovery that these muscle bands possess specific electrical properties rests on experimental evidence. If one alone of the four muscle bands is injured, either by acute or chronic ischemia, or by undue stretching, or by the application of chemicals, such as potassium chloride, a change in the electrocardiogram always occurs, and this change is always the same for a given muscle.

Can this experimental observation be correlated with the usual concepts of electrocardiograms, and also with the anatomy of the conducting system? The statement that the action current passes along the bundle of His and its branches toward the apex of the ventricles, and thence along the subendocardial network, and arrives eventually at the base of the interior of the ventricles is consistent with our knowledge of ungulate cardiac anatomy. The theory of radial penetration is not consistent with known anatomy. We have shown in the beef heart that, in its final distribution, the Purkinje cell is parallel to the muscle fiber. If there were only radial penetration of the action current in all parts of the heart, there would have to be radial penetration of the conducting tissue, whatever the histologic structure of this conducting tissue. In no heart does

any considerable portion of the Purkinje tissue penetrate radially, and in no heart does ordinary muscle fiber penetrate radially from endocardium to epicardium except at the apex. Even if one were to suppose that the action current passes longitudinally in some muscle fibers and transversely in others, the connective tissue barriers which separate layers with unlike blood supply are still to be considered.

The fact that the electrocardiograms of ungulates possess positive and negative waves which are similar to those of man (and dogs) suggests that the conduction pathways, whatever their histologic structure may prove to be, are similarly arranged in the two orders.

If, in man, it were proved that there is a conducting pathway (special tissue, or ordinary muscle, or even nerves) with a distribution similar to that of the Purkinje system in ungulates, the classical statement that the action current passes along the bundle, its branches, and the subendocardial network would be given anatomic support which it lacks at present. Our experiments have led us to suggest that the action current is distributed to each ventricular muscle individually, and that, where the wall is thin, as at the apices, the trabeculated area, and the pulmonary conus, the pathways are demonstrably shorter. The pathway to the deeper muscles at the base of the ventricles is longer, so that the negativity must be later. The sheaths separating these muscles, which need not be conspicuous to prevent spread of current, may prove to be the critical factor in explaining the electrical changes which are characteristic of a lesion limited to a single muscle band.

4. Function.—Harvey[31] and Borelli[32] thought that "the true action of the muscle of the heart is the contraction of the ventricles and the compression and expression of the blood contained in them." Both Pettigrew[33] and Tandler[4] discussed function, but the most detailed suggestions were made by Keith[1] and Flett.[5] Haycraft[34] and Krehl,[35] in the same year, described two fulcrums of the heart—one fixed by mediastinal attachments, and another (apical) which is active by virtue of the fact that the longitudinal fibers of the superficial muscles which run up to the A-V ring do not cause shortening of the septum from apex to base, but, when contracted, fix the apex and prevent its bulging and rupture. Inasmuch as the exterior portions of the superficial muscles are oblique, they do not cause apex to base shortening but do produce a certain rotation of the apex. Flett[5] affirmed this explanation.

Certain facts are well established. The superficial muscles possess an internal portion which constitutes the papillary muscles. Physiologists agree that the time of initial negativity at the interior and exterior of the apices of the two ventricles is early. Recently Rappaport and Sprague[36] reported that heart sounds were present during the period of isometric contraction. These facts give anatomic and physiologic support to the conception that the superficial muscles have two definite functions, namely (1) to fix the apical fulcrum, and (2) to fix the A-V valve leaflets. It would be impossible to have a period of rising tension with

isometric contraction unless the ventricular cavity were closed. In order to close the ventricular cavity, both the semilunar and A-V valves must be in firm apposition. To prevent the A-V valves from bulging into the auricles, thus allowing regurgitation, the valve leaflets must be fixed, and, to accomplish this, the papillary muscles must be contracted in order to keep the chordae tendineae tense. Early contraction of these superficial muscles also seems necessary if one is to explain why the apical area does not normally bulge outward to form an aneurysm, for, in some places, the wall is scarcely 1 mm. thick.

Two clinical observations can be explained if this is the function of these muscle bands. First, a mitral murmur sometimes develops after apical infarction. It is probable that this is due to inadequate tension of the damaged muscle on the valve leaflet, rather than to dilation of the rather heavy fibrous rings at the base of the heart. Second, when an apical aneurysm has developed, and this predicates damage of the two superficial muscles, the thinned apex does bulge during systole. This is also consistent with the observation that, in high-grade mitral stenosis, with calcification, when the left intraventricular pressure is low, the papillary muscles are small, whereas, in conditions such as hypertension and aortic stenosis, in which intraventricular pressure is abnormally increased, the papillary muscles are commonly hypertrophied. The same type of analysis applies to the right side of the heart.

The deep sinospiral muscle forms the main mass of the right ventricle, and must be responsible for maintenance of the pulmonary circulation. When this muscle fails, right-sided heart failure occurs. The left portion of this muscle is also large and, because of the direction of its fibers, can have no other function than expulsion of blood. When this muscle is injured, either in the right or the left portion, a considerable fall of blood pressure takes place.

Hesse,[37] Krehl,[35] and Flett[5] thought that the deep layers take the blood which has been "wrung" out of the lower third of the heart and force it into the aorta. In 1921, Samways[38] and Campbell[39] stated that, structurally, the semilunar valves are not competent to close the aortic orifice against the elastic recoil of the aortic wall, and insisted that some other mechanism must support these valves. The only structure in an anatomic position to do this, according to Flett,[5] is the deep bulbospiral muscle, and he emphasized the probability that it contracts later than the other muscle fibers. If the deep bulbospiral contracted early, it would produce narrowing of the aortic outlet, and this would be equivalent to aortic stenosis. Since it contracts late, it completes the emptying of the ventricle, supports the blood column in the aorta, and, when it relaxes, the aortic valves fall back into position and maintain the diastolic pressure. Presumably, the period of isometric relaxation is that period when the superficial muscles which first went into contraction are recovering, and before the deep sinospiral and (on the left) the deep bulbospiral have relaxed sufficiently to allow differential pressures to

open the A-V valves. According to this explanation, the deep bulbospiral recovery phase would end at a variable time after the second sound, i.e., it would vary with the filling of the heart, the tension developed, and the nutrition of the muscle and its mass; this would account for the well-known inconstancy of the relation of the second sound to the end of the T wave of the electrocardiogram.

SUMMARY AND CONCLUSIONS

Observations on the structure of the heart made by anatomists during the past five centuries have been reviewed. From these numerous sources certain conclusions are drawn:

1. The mammalian ventricle is composed of several separate muscles.

2. If heart muscle is examined in cross section, connective tissue sheaths are seen between various planes of contractile tissue. Work is now in progress in the hope of ascertaining whether these sheaths extend throughout the course of a given muscle band.

3. Functionally, coronary arteries are end arteries.

4. We have suggested, and Lowe has confirmed, that each ventricular muscle has its own source of blood supply under normal conditions. These conditions may be disturbed if side pressures are lowered by disease processes, for then the small anastomotic channels open. Normally, these channels are present but nonfunctioning.

5. It is known that, in the beef heart, each of the four main ventricular muscles has a direct Purkinje supply, only a small portion of which penetrates radially from the endocardium toward the epicardium. Work is in progress to ascertain whether, by the reconstruction of serial sections of small human hearts, the existence of a distributing system can be demonstrated.

6. Many types of experimental procedures have proved that damage to a given ventricular muscle produces a constant and characteristic change in the electrocardiograms of dogs, monkeys, cats, and rabbits. The full explanation of these changes, which we have also observed in man, and which Lowe has seen, has been difficult to reconcile with the generally accepted theories of electrocardiography which ignore the presence of connective tissue sheaths separating muscle layers with different blood supplies; these sheaths set up a boundary between normal and damaged tissue.

7. Anatomists of note agree that these ventricular muscles have specific functions; the superficial muscles fix the fulcrums so that the septum and the weak-walled apices do not bulge during systole. They also fix the auriculoventricular valve leaflets, and thus prevent regurgitation into the auricles during ventricular systole.

8. The deep sinospiral muscle has an expulsive function and maintains the pulmonary circulation. Its left portion also plays an important part in emptying the left ventricle.

9. The deep bulbospiral muscle provides expulsive force for the left ventricle and is essential in maintaining the aortic pressure toward the end of systole.

10. In experimental animals, survival is possible if both superficial muscles and/or the deep sinospiral are injured. When the deep bulbospiral is damaged the animals never survive.

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THE SYNDROME OF RUPTURE OF AN AORTIC ANEURYSM INTO THE PULMONARY ARTERY

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A REVIEW of the current textbooks of medicine, physical diagnosis, and cardiology reveals a paucity of accurate data on the clinical course and physical phenomena of a fistulous opening between an aortic aneurysm and the pulmonary artery. Hope[1] studied a patient who was admitted to the Edinburgh Infirmary, Oct. 30, 1833, and subsequently described the clinical features, physical phenomena, and post-mortem observations in a report entitled: "Case of Rupture of a Dilated Aorta Into the Pulmonary Artery." Hope's description of the syndrome is so nearly perfect that it is difficult to understand why it has been practically ignored by subsequent writers.

After Hope's report, the next most comprehensive review is that by Peacock,[2] in 1868. He collected eighteen cases from published reports and added one case of his own. In 1907, Kappis[3] again reviewed the previously reported cases, thirty-two in number, and discussed his personal experience in one case.

A review of the literature since Kappis' publication reveals scattered case reports,[4-9] but no attempt by the authors to define a syndrome comparable to that described by Pepper and Griffith,[10] in 1890, which accompanies the establishment of a fistulous connection between an aortic aneurysm and the vena cava.

The three cases which are here reported were studied by many observers, and, although there was no uniformity of opinion, the symptoms and signs were similar in their essential aspects in all of them. The differences were attributable to variations in the size and location of the aneurysms, the size of the fistulous openings, and the associated cardiovascular disease. In the first case, which was observed in 1929, the correct diagnosis was not made, but it was specifically noted that the physical phenomena and clinical course were not in keeping with the diagnosis of uncomplicated aortic regurgitation and aortic aneurysm. The second patient, who was studied in 1937 and 1938, had a conditional diagnosis of a fistulous opening into the pulmonary artery. In the third case there was an unconditional diagnosis of this complication of aortic aneurysm.

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CASE REPORTS

CASE 1.—G. Z., aged 55 years, a white, male farmer, was admitted to the Medical College of Virginia Hospital Feb. 23, 1929.

History.—He complained of an indefinite pain in the upper and anterior part of the right side of the chest, cough, and breathlessness. Three weeks previously he had been ill from an attack of "influenza." During this illness he suffered pains in his back and limbs; his cough was troublesome; and he had fever for one week. He was confined to bed for two weeks. Three days before he entered the hospital the pain in the right side of the chest became worse, and dyspnea was so severe that he could rest only when he was propped up in bed. Nothing significant was revealed in the past history or family record.

Physical Examination.—The patient was a well-nourished and well-developed man in an orthopneic position. There was moderate cyanosis of the lips, mucous membranes and finger tips. His temperature was 98° F.; his pulse rate, 70 to 80 per minute; and his respiratory rate, 22 to 26 per minute. The pupils were equal, and their reaction was normal. The ears, nose, and mouth were normal. The neck veins were markedly distended, even in the orthopneic position. The thorax was barrel-shaped, and hyperresonant to percussion except over the bases, where the percussion note was dull. Medium, moist râles were heard over the bases posteriorly, and the breath sounds were generally suppressed; the physical phenomena indicated emphysema, with mild pulmonary stasis and a moderate effusion in the right pleural cavity. There was a definite increase in supracardiac dullness. The right cardiac border was not definitely located, but the apex beat and point of maximum intensity were in the sixth intercostal space, 12.2 cm. from the midsternal line. Over the base of the heart, in the left second and third intercostal spaces, 1 to 2 cm. from the sternal margin, a distinct systolic and a less distinct diastolic thrill could be felt. Over this same area, with the maximum intensity 2 cm. to the left of the sternal margin in the third intercostal space, a whirring systolic and diastolic murmur was heard. The murmur was "quite similar to that occurring in patients with patent ductus arteriosus." The systolic phase was harsher, louder, and of greater duration than the diastolic. There was a systolic apical murmur, but no diastolic murmur was heard. The second sounds were not significantly altered. The blood pressure was 105/30 in each arm, and 140/35 in the right leg. The pulse was of the Corrigan type. The abdomen was moderately distended, suggesting ascites. The liver was enlarged and tender. There was moderate edema of the ankles.

Laboratory Examination.—The blood Wassermann reaction was strongly positive. Examination of the blood showed: Erythrocytes, 5,100,000; hemoglobin, 91 per cent; leucocytes, 8,750; neutrophiles, 70 per cent; lymphocytes, 19 per cent; monocytes, 11 per cent. The specific gravity of the urine was 1.022, and there were occasional granular casts. Roentgenographic study: "The patient has a saccular aneurysm the size of an orange extending forward and to the right from the ascending portion of the aorta. The heart is mitral in shape, and moderately enlarged. There is moderate pulmonary congestion, and a small amount of fluid in the right pleural cavity."

Clinical Diagnoses.—(1) Aneurysm of the ascending aorta; (2) congestive heart failure, preponderantly of the right ventricle; (3) "The diastolic murmur and vascular phenomena suggest aortic insufficiency, but this diagnosis is not in keeping with the manifestations of right-sided heart failure. Cor pulmonale is suggested by the manifest emphysema and bronchiectasis."

Course.—The patient became more cyanotic and breathless, regardless of energetic treatment. He died March 4, 1929.

Autopsy (partial).—Only the heart was removed for examination by Dr. L. C. Pusch (Fig. 1).

The specimen consisted of a heart with the entire aorta attached. It was not weighed because of the large amount of aorta and aneurysm attached. The heart appeared only slightly enlarged. The left ventricular wall measured 16 mm. in thickness; the right, 6 to 9 mm. All of the valve rings were competent, and the leaflets were thin, smooth, and pliable. The entire ascending portion and part of the transverse portion of the aortic arch were greatly dilated in a single large saccular aneurysm which measured 12 by 9 by 5 cm. This arose 5 mm. above the commissures of the aortic valve leaflets and extended to the origin of the left subclavian artery. The innominate artery and the left common carotid artery arose from the aneurysmal sac, and the left subclavian arose from the undilated aorta.

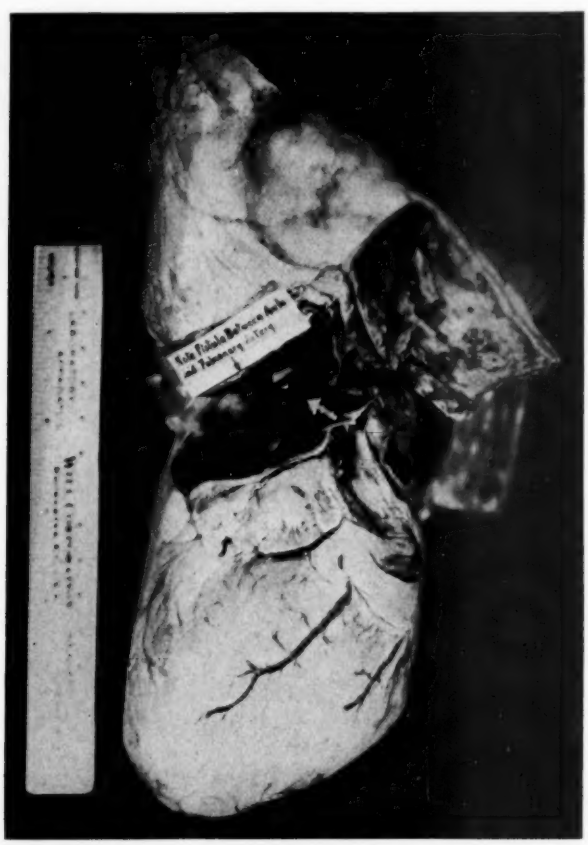

Fig. 1.—Case 1. The specimen is viewed from the right, showing the right ventricular enlargement. The pulmonary artery has been opened, exposing the fistula.

Much of the aneurysmal sac was filled with old, laminated thrombus and blood clot. Two and one-half centimeters above the aortic valve commissures, on the left side of the aneurysm, there was a rough, ovoid opening in the wall of the aneurysm which measured 1 by 1.2 cm. This fistula opened into the pulmonary conus at a point 2.5 cm. above the commissures of the pulmonic valve.

CASE 2.—W. R. D., a white man, aged 50 years, was first admitted to the medical service of the Medical College of Virginia Hospital Dec. 26, 1937, and discharged Jan. 23, 1938.

History.—The patient had been a reporter for twenty years, but, because of economic difficulties, he had moved to the country in April, 1937. He noticed some breathlessness when he began farm work, but this was attributed to smoking and unaccustomed physical activity. He was definitely restricted in his activities by fatigue and breathlessness, but he continued to work, with moderate limitations. On Dec. 18, 1937, while pitching hay in the barn, he was seized with a constricting sensation over the anterior part of the thorax. This was associated with a pounding in his chest and severe dyspnea. The dyspnea became progressively worse and was continuous, and there was a hacking, nonproductive cough. By December 23 he had become orthopneic. He was uncomfortable in any position, and the dyspnea was so distressing that he was unable to speak or drink fluids in comfort. The past history suggested a syphilitic infection at the age of 22 years, but otherwise was not contributory.

Physical Examination.—The patient was a fairly well-developed, undernourished white man, sitting up in bed, with his head resting on a pillow placed on a bed table. The dyspnea was continuous and so severe that talking was difficult, and he avoided the slightest physical effort. The oral temperature was 99.2° F., the pulse rate 98, and the respiratory rate, 28 per minute. There was no visible cyanosis. The eyes, ears, nose, and throat were not remarkable. The cervical veins were markedly distended, and the venous pressure was 240 mm. of water. The lungs were resonant throughout. There were a few medium, moist râles over the lung bases posteriorly, and the breath sounds were distinctly harsh in quality and increased in intensity. There was a moderate increase in the width of the supracardiac dullness. The cardiac apex was seen and felt in the fifth intercostal space, and the left cardiac border was 12.5 cm. to the left of the midsternal line in the fifth intercostal space; the right cardiac border was 5 cm. to the right of the midsternal line in the fourth intercostal space. Over the base of the heart, centering at the left second and third intercostal spaces, 1 to 3 cm. from the sternal margin, a purring systolic thrill and a questionable diastolic thrill were felt. Over this same area there were a whirring, intense, systolic murmur and a less distinct diastolic murmur. The diastolic murmur was not constant except when the patient was in the erect position, and it was localized to a small area along the left sternal margin. The systolic murmur was heard over a larger area, even at the angle of the left scapula. There was no Austin Flint murmur. The aortic second sound was slightly amphoric in quality, and of normal intensity, but the pulmonic second sound was markedly increased in intensity. The pulse was rhythmic and typically Corrigan in type. The blood pressure was 140/40-20, and a snapping sound could be heard to the zero point on the manometer. The liver was tender and extended 6 cm. below the costal margin. There was edema of the sacral area and the lower extremities.

Laboratory Examination.—The blood Wassermann and Kline reactions were positive. Examination of the blood showed: Erythrocytes, 3,420,000; hemoglobin, 70 per cent; leucocytes, 9,750; neutrophiles, 79 per cent; lymphocytes, 17 per cent; and monocytes, 4 per cent. The urine was normal. Roentgenographic study: "The teleroentgenogram showed the heart 18.2 cm. in transverse diameter with a cardiothoracic ratio of 59 per cent. The aorta in its ascending portion was moderately increased in diameter, but there was no sacculation. The heart was mitral in shape. There was moderate pulmonary stasis" (Fig. 2). Electrocardiographic study showed sinus tachycardia; the rate was 115 per minute (Fig. 3). The kymograph is shown in Fig. 4.

Clinical Diagnosis.—Syphilitic aortitis, with aortic insufficiency. "This diagnosis is, however, debatable for the following reasons: (1) The dyspnea is continuous and intense, not paroxysmal; (2) The murmur is at times continuous, and the systolic murmur dominates the auscultatory phenomena; (3) The failure is predominantly right-sided, like that of mitral disease; (4) There is no Austin Flint murmur; (5) The roentgenograms and electrocardiogram are not indicative of aortic valve insufficiency."

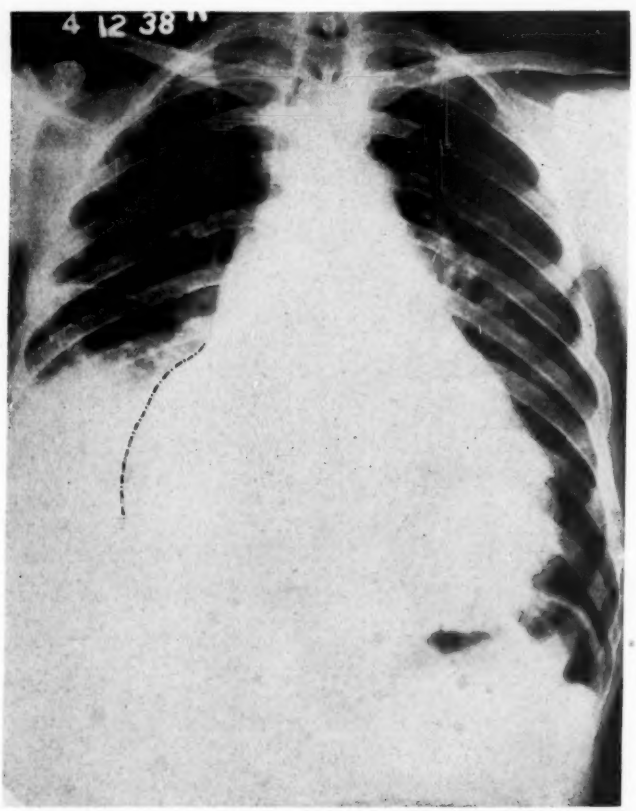

Fig. 2.—Case 2. Teleroentgenogram showing a "mitral" configuration, and marked right ventricular enlargement.

Hospital Course.—Digitalis was administered in adequate quantities, with only slight improvement. On Dec. 29, 1937, phlebotomy was done; 500 c.c. of blood were removed, but with only moderate relief of the dyspnea. On Jan. 9, 1938, the patient was started on a series of intravenous injections of mercurial diuretics. From this point improvement was rapid, and the patient was discharged on the twenty-eighth hospital day as an ambulatory patient to the cardiac clinic. When he left the hospital, all objective signs of congestive failure had disappeared, but physical activity easily induced breathlessness. He was observed in the outpatient clinic at weekly intervals from Feb. 18, 1938, to April 4, 1938. During this period he continued to take digitalis and restricted his exercise.

Second Hospital Admission.—He was readmitted April 5, 1938. During this hospital stay the clinical course was characterized by moderate breathlessness, but

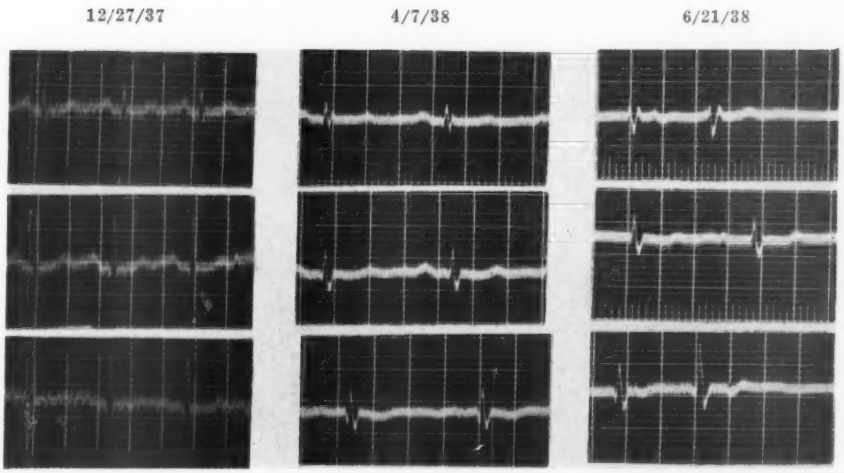

Fig. 3.—Case 2. The electrocardiogram shows transition from a normal axis to a right axis deviation.

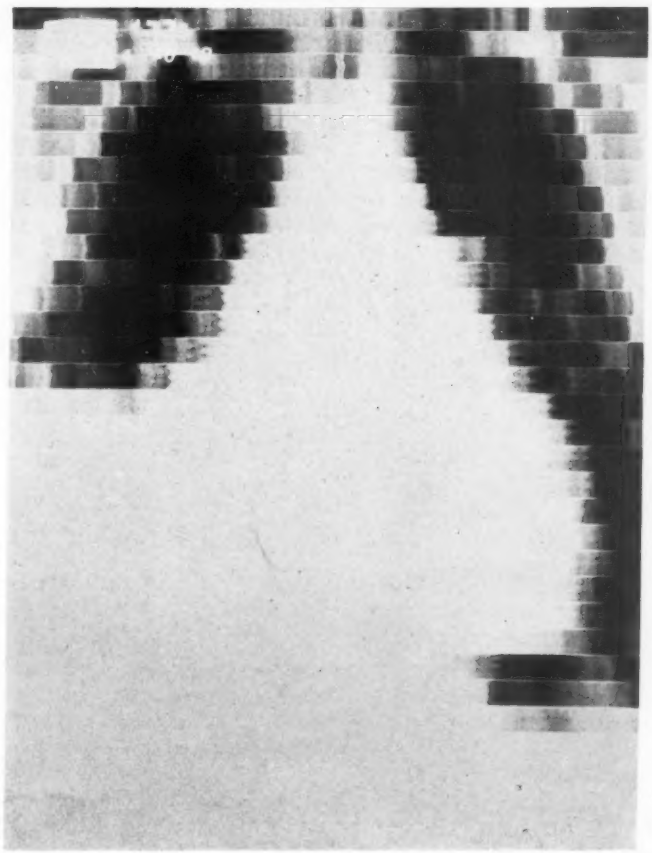

Fig. 4.—Case 2. Kymogram shows wide amplitude of the contraction waves, suggesting aortic insufficiency.

it was never so severe as that suffered during the early period of the first hospital stay. High venous pressure, with hepatic enlargement, edema, and ascites, characterized the clinical picture. The phenomena of pulmonary edema were conspicuous by their absence. Recurring effusion into the right pleural cavity required aspiration, as follows: 1,000 c.c. on July 4; 900 c.c. on June 9; 1,700 c.c. on June 17; and 1,750 c.c. on June 25; making a total of 4,350 c.c. The physical signs over the heart, and the blood pressure, were similar to those recorded previously. In spite of active therapy, the congestive heart failure did not improve, and the patient died June 28, 1938.

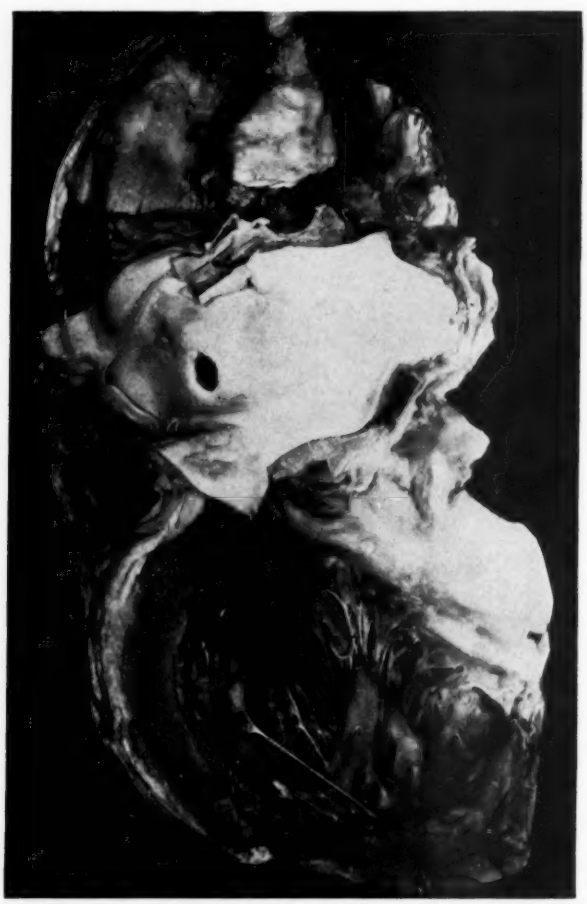

Fig. 5.—Case 2. The specimen shows the thickened right ventricle and the fistula into the pulmonary artery.

Final Diagnoses.—(1) Syphilitic aortitis involving the base of the aorta; (2) aneurysm of the ascending aorta; (3) aortic insufficiency(??); (4) fistula between the aortic aneurysm and pulmonary artery(?); (5) congestive heart failure, predominantly right-sided; (6) cardiac cirrhosis of the liver.

The autopsy was performed by Dr. Paul Kimmelstiel.

Anatomic Diagnoses.—(1) Right-sided hydrothorax, ascites, and edema; (2) collapse of the right lower lobe; (3) "nutmeg" liver, with beginning atrophic cirrhosis; (4) fistulous opening between an aortic aneurysm and the pulmonary artery (Fig. 5).

Heart and Aorta.—The heart was not weighed because the aorta, with the aneurysmal sac, was left attached to the heart.

Measurements.—Left ventricular wall, 1.5 cm.; right ventricular wall, 0.8 cm.; pulmonary ring, 7.0 cm.; aortic ring, 8.0 cm.; mitral ring, 12.0 cm.; tricuspid ring, 11.0 cm.

The heart was enlarged and its apex rounded, and the epicardium was smooth, moist, and glistening. Both ventricles were dilated and the walls hypertrophied, the right ventricle much more so than the left. The papillary muscles of the left ventricle and the trabeculae carneae were somewhat flattened; those in the right ventricle were markedly rounded and hypertrophied. The endocardium appeared normally firm, and free from foci on the cut surface. A rough, ante-mortem thrombus was found in the left auricular appendage. The commissures and valve leaflets of all cusps and valves appeared normal and delicate. The chordae tendineae appeared to be normal. The right coronary ostium was slightly narrowed by changes in the aortic wall, but the ostium of the left coronary artery was normal. The lumina of both coronary arteries were patent throughout; the walls were elastic, and the intima showed slight arteriosclerotic changes.

The entire ascending aorta bulged out anteriorly into a saccular aneurysm, the diameter of which was approximately 10 cm. The intimal surface was irregularly roughened by numerous atherosclerotic plaques, and by extensive longitudinal wrinkling. The wrinkling and irregular thickening of the aortic wall were present in the arch of the aorta, and descended as far as the beginning of the abdominal aorta, at which point the change in the aortic wall stopped abruptly.

There was a fistula between the pulmonary artery and the aorta which measured approximately 0.7 cm.; it was circular, and almost punched out in appearance. It was situated approximately 3 cm. from the aortic ring and 1.5 cm. above the pulmonary ring. There were two areas of scarring in the pulmonary artery next to the fistula, one immediately to the left of the opening of the fistula, and the other approximately 1 cm. to the right of the fistula; both scarred areas measured approximately 1 cm. in diameter and were irregular in outline.

CASE 3.—G. W., aged 58 years, a negro truck driver, was admitted to St. Philip Hospital Sept. 3, 1940.

History.—Approximately three weeks previously, his illness began with breathlessness which was sudden in onset and progressive in intensity. One week before he entered the hospital, dyspnea became so severe that he remained in bed in an orthopneic position, but with only partial relief. There had been no cardiac or thoracic pain, and only a mild, nonproductive cough. Swelling of the ankles was first noticed two weeks previously, and for one week the abdomen had been swollen and tender. His previous health had been normal except for a dry cough of five weeks' duration, accompanied by hoarseness and difficulty in swallowing; he attributed this to a "cold." Nothing significant was revealed in the past history or family record.

Physical Examination.—The patient was a well-nourished and well-developed man in an orthopneic position. There was no cyanosis. The temperature was 99° F.; the pulse rate, 105; and the respiratory rate, 31 per minute. The pupils were equal, and their reaction was normal. The arteries of the fundi showed a moderate degree of arteriosclerosis. The ears, throat, and mouth were not unusual. The patient was hoarse and his cough was brassy in quality, suggesting recurrent laryngeal nerve paralysis and tracheal compression. The neck veins were distended 4 cm. above the jugular bulb in the orthopneic position. The thorax was normal in shape, and was resonant except over the right base, where the percussion note was dull. A few medium, moist râles were heard over the lower lung lobes posteriorly,

and the breath sounds over the hilar area were high pitched; both inspiration and expiration were moderately prolonged, suggesting bronchial compression. In the right second and third intercostal spaces there was a visible and palpable pulsation. There was a definite increase in supracardiac dullness. The cardiac apex was seen and felt in the fifth intercostal space, and the left cardiac border was 13 cm. to the left of the midsternal line. The right cardiac border was not definitely located. Over the base of the heart, centering at the left third intercostal space, 3 cm. from the sternal margin, there was a purring systolic and diastolic thrill which was most distinct during the systolic phase. Over this same area there was a harsh, whirring, continuous murmur which was distinctly "cogwheel" in quality. The systolic phase was more intense and of longer duration than the diastolic. The diastolic murmur was transmitted only a few centimeters along the left sternal margin. There was no Austin Flint murmur. The aortic second sound was moderately accentuated and was amphoric in quality, and the pulmonic second sound was definitely accentuated. The pulse was rhythmic and typically Corrigan in type. The blood pressure was 190/50-40. The liver was tender and extended 8 cm. below the costal margin. There was edema of the sacral area and the lower extremities.

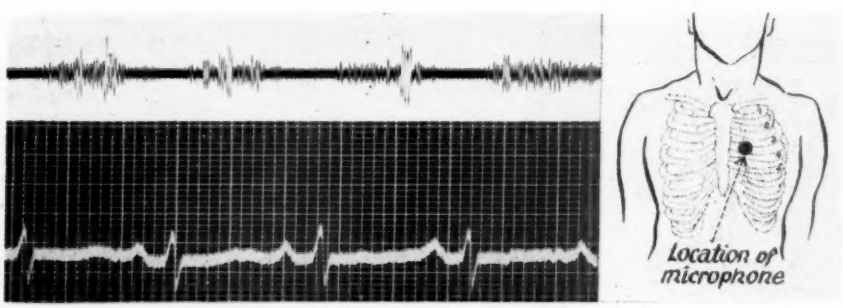

Fig. 6.—Case 3. Stethogram shows a continuous murmur with systolic accentuation.

Laboratory Examination.—The blood Wassermann and Kline reactions were positive. Examination of the blood showed: Hemoglobin, 69 per cent; erythrocytes, 3,900,000; leucocytes, 11,600; neutrophiles, 70 per cent; lymphocytes, 18 per cent; monocytes, 10 per cent; and eosinophiles, 2 per cent. The urine was normal. Chemically, the blood was normal. Roentgenographic study: "A teleroentgenogram showed that the transverse diameter of the heart was 16.7 cm., and the transverse diameter of the thorax, 31 cm. The cardiothoracic ratio was 53 per cent. The transverse diameter of the great vessels was 14.2 cm. There were multiple saccular aneurysms of the ascending, transverse, and descending aorta. The saccular aneurysm, which was 7 cm. in diameter, at the right mediastinal margin showed a marked expansile pulsation. There were also saccular aneurysms of the transverse and descending portions. There were marked mottling of the vascular markings of both lungs and moderate pleural effusion at both costophrenic angles. Esophagrams showed pressure of the aneurysmal aorta on the esophagus. The lower half of the esophagus was flattened and displaced to the left and posteriorly. The kymogram showed expansile pulsation of several saccular aneurysms." Electrocardiographic study showed sinus tachycardia, rate 107; diphasic T in Leads I, II, and III, suggesting digitalis effects; left axis deviation; axis, -40. The stethogram showed a continuous murmur with a systolic accentuation (Fig. 6).

Clinical Diagnoses.—(1) Syphilitic aortitis with saccular aneurysms; (2) fistulous communication between aortic aneurysm and the pulmonary artery; (3) congestive

heart failure, predominantly right-sided; (4) tracheal compression, with atelectasis of the lower lobes of the lungs.

Hospital Course.—Digitalis, diet restrictions, and diuretics gave only partial relief. The venous pressure continued high, varying from 130 to 200 mm. of water. The edema of the lower extremities increased and bilateral pleural effusion developed but never became sufficiently large to require aspiration. Ascites did not develop. Orthopnea was continuous, and it was only partially relieved by oxygen therapy and opiates. Death occurred on Nov. 7, 1940, from respiratory difficulty and heart failure.

The autopsy was performed by Dr. John S. Howe.

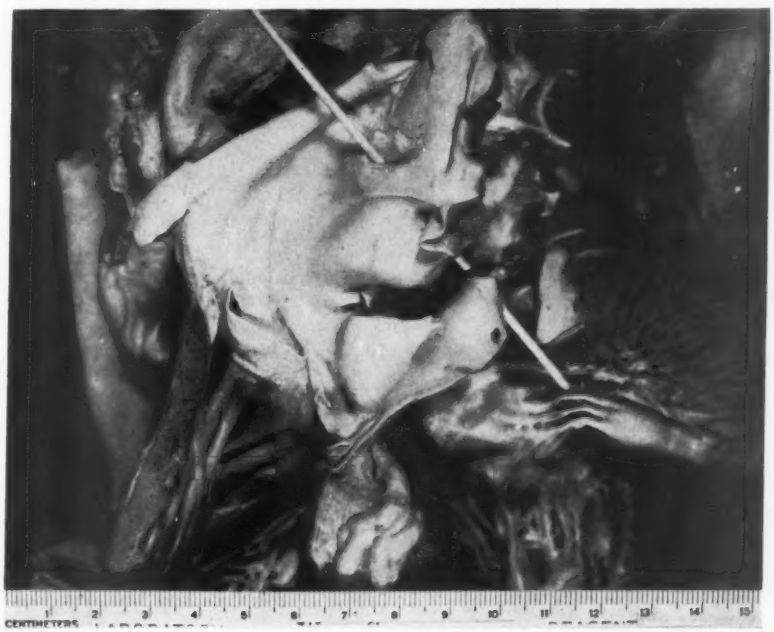

Fig. 7.—Case 3. The specimen shows the slitlike opening into the pulmonary artery. (The specimen was mutilated through error.)

Anatomic Diagnoses.—(1) Atelectasis of the right lower lobe; (2) atherosclerosis of the aorta; (3) syphilitic aortitis; (4) passive congestion of the liver and kidneys; (5) hydrothorax on the right; (6) early stage of nutmeg liver; (7) fistulous opening between an aortic aneurysm and the pulmonary artery (Fig. 7).

Heart and Aorta.—The heart was moderately enlarged; the right ventricle was somewhat larger than the left. The left ventricular wall measured 2.2 cm., and the right ventricular wall, 1 cm., in thickness. The aortic valve ring was 7 cm. in circumference, and the pulmonic, 6.5 cm. The mitral, tricuspid, and pulmonic valve leaflets were thin and translucent. The aortic valve leaflets were thin and pliable, with sharp, free margins. There was slight separation of the aortic leaflets by a whitish translucent plaque at one commissure, and there was fusion of another commissure. There was partial fusion of two of the valve leaflets for a distance of 5 mm. from the commissures. The aorta just beyond the valve ring was diffusely dilated, and its intima showed marked longitudinal wrinkling, scarring, and whitish and yellowish translucent plaques. This diffuse dilatation involved the whole arch of the aorta to a point 12 cm. beyond the origin of the left subclavian artery. In ad-

dition to diffuse saccular dilatation of the arch of the aorta, there was a saccular dilatation which arose at a point 6.5 cm. above the aortic ring and communicated by a narrow ostium, 3.5 cm. in diameter, with the aorta. In this saccular dilatation, which was anterior to the aorta and on the posterior surface of the pulmonary artery, there was a slitlike perforation 1 cm. in length and 2 mm. in width. This opened into the pulmonary artery at a point 4.5 cm. above the pulmonic valve ring. There was another, smaller, saccular aneurysm at the transverse part of the arch, lying above the arch of the aorta. Its opening measured 3 cm. in diameter, and from it arose the innominate artery and the left common carotid artery. The left subclavian arose from the main aorta at a point 1.5 cm. beyond the opening of this saccular aneurysm.

COMMENTS

Opinions concerning the prognosis of rupture of an aortic aneurysm into the pulmonary artery have been characterized by great variation. Osler and McCrea,[11] in discussing the complications of aortic aneurysm, said: "The sack may rupture into the pulmonary artery, producing instantaneous death." On the other hand, Clere, et al.,[12] reported a patient who supposedly lived for more than four years.

CASE NUMBER	AGE	LOCATION OF ANEURYSM	SIZE AND SHAPE OF FISTULA	DURATION OF ILLNESS
1.	55	ascending aorta	 1 x 1.2 cm.	4 wks., +- days
2.	50	ascending aorta	 0.7 cm.	8 mos., +- days
3.*	58	multiple large aneurysms of ascending and transverse aorta	 1 cm. x 2 mm.	2 mos., +- days

*Complicated by essential hypertension

Fig. 8.

It is apparent that each case is a specific problem, for the factors which decide the duration of life are the size and the number of aneurysms, the size of the fistulous opening, the extent of the associated cardiovascular disease, and the efficiency of the therapy. Fig. 8 attempts to summarize these factors as they concern the cases here reported. It is significant that in Case 2 the patient was relieved of all active symptoms for a period of approximately six months. In this case the location and size of the aneurysm were such that it did not compress any vital mediastinal structure; the fistulous opening was of moderate size (0.7 cm. in diameter), and there was no complicating cardiovascular disease.

At autopsy, right ventricular hypertrophy and dilatation were striking in each of the three cases here reported. Stevenson found marked

hypertrophy in two cases and a normal right ventricle in a third case. In the two cases in which there was right ventricular enlargement, the fistulous opening was "large," whereas, in the third case, in which there was no enlargement of the right ventricle, the opening was "very small." In the case reported by Peacock, there was, in addition to the fistulous opening into the pulmonary artery, disease of the aortic valve which he concluded resulted in aortic regurgitation. In commenting on the size of the heart, he emphasized the fact that the enlargement of the right ventricle was greater than is usually found in uncomplicated aortic regurgitation.

An explanation for the stress which results in right ventricular enlargement is obscure and cannot be finally ascertained without carefully controlled animal experiments. It would seem obvious that a fistulous connection between the aorta and the pulmonary artery would result in a great increase in the pressure in the pulmonary artery; yet the observed facts do not bear out this conclusion. Blalock[13] and his associates have anastomosed the subclavian artery to the pulmonary artery in dogs, and in this experiment there was no rise of the pressure in the pulmonary artery. It is safe to predict that there can be a very great increase in the minute volume of blood passing through the lesser circulation without a corresponding rise in pulmonary arterial pressure, provided the left ventricle remains efficient. In the above experiment the current of blood from the subclavian artery entered the pulmonary artery in the direction of the pulmonary blood flow; and, if a current of blood is shunted from the aorta, a high pressure tube, into the pulmonary artery, a low pressure tube, in the direction of the pulmonary current, the pressure proximal to the point of entrance is reduced by the suction effect of the high tension current. On the other hand, if the current from the aorta enters at a right angle to the pulmonary current or is directed toward the right ventricle, an increase in pressure proximal to the fistula would result, and the right ventricle would be required to overcome this. It is quite probable that this hydrodynamic factor is the major one in connection with the enlargement of the right ventricle.

Pressure of the aneurysmal sac on the pulmonary artery, reducing its lumen, could increase the resistance to blood flow in the pulmonary artery, and result in increased right ventricular stress. The patient in Case 2 had the most striking degree of right ventricular enlargement, and the electrocardiogram strongly indicates that this developed after the establishment of the fistulous connection. Furthermore, in the cases reported by Stevenson, there was a definite relationship between the size of the opening and the size of the right ventricle.

The factors responsible for an increase in the size of the myocardium remain debatable; yet, a continuous increase in work, relative or absolute,

beyond a critical level, is the one constant factor which is found in all instances of acquired heart muscle hypertrophy. In the cases under discussion, many factors may have been concerned, but it is more than probable that the effects of the current of blood from the aorta on the pressure in the pulmonary artery proximal to the fistulous opening were the essential ones. That stress on the right ventricle existed is evidenced not only by the pathologic changes, but by the preponderance of right-sided heart failure which was such a striking feature in these cases.

Continuous and severe breathlessness was a prominent clinical feature, but observation did not indicate that pulmonary stasis (left ventricular failure) was the cause of the dyspnea and accelerated rate of respiration. In all of the cases there were basal râles, but it must be emphasized that the extent of pulmonary stasis was strikingly slight, considering the intensity of the dyspnea. Furthermore, oxygen in high concentration modified the breathlessness very little, if at all.

The establishment of a fistulous connection between the aorta and the pulmonary artery results in a great increase in the minute volume of blood passing through the pulmonary arterial tree. The magnitude of the augmented circulating volume is directly related to the size of the fistula, but it is a certainty that, as a result, there are varying degrees of engorgement of the afferent vessels, including the afferent arterioles and alveolar capillaries.

The primary stimulus of the Hering-Breuer reflex is the tension change in the lung parenchyma; and any condition, such as pulmonary engorgement, will increase the sensitivity of this reflex, resulting in rapid breathing, with dyspnea. The type of respiration and the continuous breathlessness observed in these cases suggest that this reflex mechanism is the essential factor, rather than pulmonary edema resulting from failure of the left ventricle.

The diagnosis of rupture of an aortic aneurysm into the pulmonary artery is an intriguing clinical problem. It is difficult to ascertain from a review of the reported cases how often this has been accomplished, for, in most instances, the authors do not make a definite statement. It is obvious that the probability of a correct clinical diagnosis may be influenced by many factors. The cases here reported may be a fair sample of what one might expect in others; nevertheless, it is reasonable to assume that such factors as the size of the fistula, pressure from the aneurysms, and associated cardiovascular disease could very definitely modify the clinical course.

A study of these cases shows that the symptoms and signs are characteristic. Syphilitic aortitis, with aortic regurgitation, is the one cardiac lesion which must be seriously considered in the differential diagnosis.

The similarity becomes less confusing when the entire syndrome is summarized, as follows:

1. Continuous and severe breathlessness.

2. The physical signs of pulmonary stasis which are slight in proportion to the intensity of the dyspnea.

3. Preponderance of right-sided heart failure, which develops immediately after the onset of the acute respiratory distress.

4. Cyanosis, which is not a significant phenomenon.

5. A purring systolic and diastolic thrill over the base of the heart, most intense during the systolic phase.

6. A long, harsh, continuous murmur, with the point of maximum intensity at the third intercostal space, 1 to 3 cm. to the left of the sternal margin. The systolic phase of the murmur is peculiarly harsh and long, whereas the diastolic phase is short in duration, and is transmitted downward for only a few centimeters along the left sternal margin. The murmur is best heard with the patient in a sitting posture and leaning slightly forward.

7. Absence of an Austin Flint murmur.

8. The peripheral arterial manifestations of free aortic insufficiency.

9. Physical and roentgenographic evidence of aneurysm of the ascending aorta.

10. Cardiac enlargement, but not classically aortic in type.

11. The electrical axis of the heart which may progress to right axis deviation.

12. A murmur which is similar in its essential details to that in cases of patent ductus arteriosus, as shown in the stethogram.

SUMMARY AND CONCLUSIONS

1. Three cases of aortic aneurysm opening into the pulmonary artery are reported. From a study of these cases the syndrome accompanying this complication of aortic aneurysm is constructed.

2. A tentative explanation is offered for the stress on the right ventricle which results in right ventricular hypertrophy and dilatation, and the occurrence of right-sided heart failure soon after the establishment of the fistula.

This complication of aneurysm of the aorta was correctly diagnosed by Dr. White[14] and his associates eight months before the death of a 72-year-old patient who was studied by them.

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A SIMPLE, INDIFFERENT, ELECTROCARDIOGRAPHIC ELECTRODE OF ZERO POTENTIAL AND A TECHNIQUE OF OBTAINING AUGMENTED, UNIPOLAR, EXTREMITY LEADS

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INTRODUCTION

ELECTROCARDIOGRAMS obtained with standard leads represent, in reality, a combination of two graphs, one from each of the extremities being utilized.[1] The standard limb leads are, therefore, bipolar extremity leads. It would therefore seem plausible that electrocardiograms which represent the potential variations of only one region of the body would lend themselves to interpretation and analysis more readily than the standard lead electrocardiograms. Such is practically the case when precordial leads are used. However, in order to obtain unipolar extremity leads (electrocardiograms that represent the potentials of only *one* extremity), special apparatus, more or less complicated, has been required. In one of the methods[2] the patient is immersed in a water bath. Another technique, devised by Wilson et al.,[3] is less complicated; the extremities are connected to a central terminal through fixed resistances of 5,000 ohms each.

Recently we have been making a study of extremity potentials (using a Wilson assembly), and, in the course of our work, devised a simple indifferent electrode of zero potential (which can be constructed in a few minutes at a cost of less than 10 cents) and a technique of obtaining "augmented" unipolar extremity leads.

CONSTRUCTION OF THE INDIFFERENT ELECTRODE

Three single lengths of ordinary electric wire and four battery clips are needed. The wire should be approximately 4 feet in length. (1) Take the three lengths, expose their ends, join as in Fig. 1, and apply one of the clips. (2) To the other ends of the wires tips can be soldered, the other battery clips attached, or such attachments made as are necessitated by variations in the construction of the electrodes of different kinds of electrocardiographs.

TECHNIQUE OF OPERATION

Precordial Leads.—(1) Set the lead switch for Lead I. (2) Place electrodes on the patient's right and left forearms and left leg, using a suitable jelly or paste on

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the skin. (3) Attach the indifferent electrode as illustrated in Fig. 2. (4) Attach the *RA* lead wire (from electrocardiograph) to the central terminal, *T*. (5) Attach the *LA* lead wire to the precordial electrode and apply where desired. (6) Standardize the electrocardiogram in the usual manner and make the record. In the

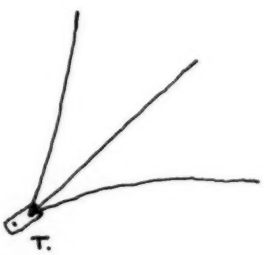
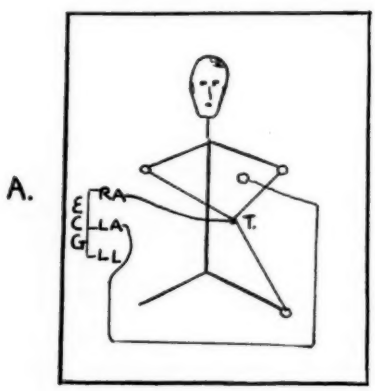
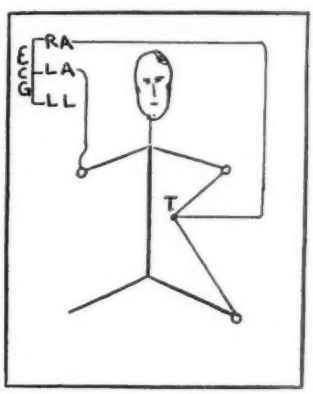
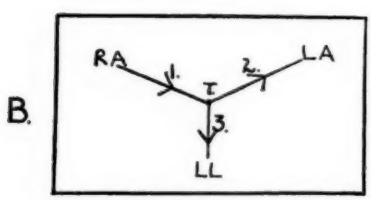


Fig. 1.—Three single lengths of ordinary (No. 18) electric wire, joined to form an indifferent electrode of zero potential. *T*, Central terminal.







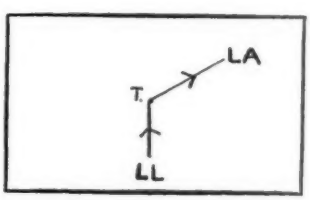


Fig. 2.

Fig. 3.

Fig. 2.—*A*, Indifferent electrode connected to take a precordial lead. (The electrocardiograph is set for Lead I.) Wilson's or the author's indifferent electrode may be used. *B* illustrates the hypothetical current flow through the indifferent electrode at a given instant. The arrows indicate direction of current flow.

Fig. 3.—*A*, Indifferent electrode connected to take the "augmented" right arm lead (the aVr lead). The electrocardiograph is set for Lead I. The author's or Wilson's indifferent electrode may be used. *B* illustrates the hypothetical current flow through the indifferent electrode at a given instant. The third end of the indifferent electrode (not drawn) is left free.

finished record, positivity will be denoted by an upward deflection, as recommended by the American Heart Association. If the switch is set for Lead II, connect the *LL* lead wire instead of the *LA* lead wire to the precordial electrode. If the switch is set for Lead III, connect the *LA* lead wire instead of the *RA* lead wire to the central terminal, and the *LL* lead wire to the precordial electrode.

For unipolar extremity leads two techniques are available.

A. Augmented Unipolar Extremity Leads

"Augmented" Right Arm Lead (aVr Lead).—(1) Set the switch for Lead I. (2) Place electrodes on the patient's right and left forearms and left leg. (3) Attach the indifferent electrode as illustrated in Fig. 3. (4) Attach the *RA* lead wire to the central terminal. (5) Attach the *LA* lead wire to the electrode on the right forearm. (6) Standardize the electrocardiogram as usual, and make the record. In the finished record, positivity will be represented by an upward deflection, and, despite the standardization, 1.5 cm. ≡ 1.mv. (see below for explanation).

To record the "augmented" left arm lead (aVl lead), connect two ends of the indifferent electrode to the electrodes on the right forearm and left leg (the third end of the indifferent electrode is left loose).

To take the "augmented" left leg lead (aVf lead), attach the indifferent electrode to the electrodes on the right and left forearms.

With this technique for augmented unipolar extremity leads, always leave the indifferent electrode off the extremity being recorded.

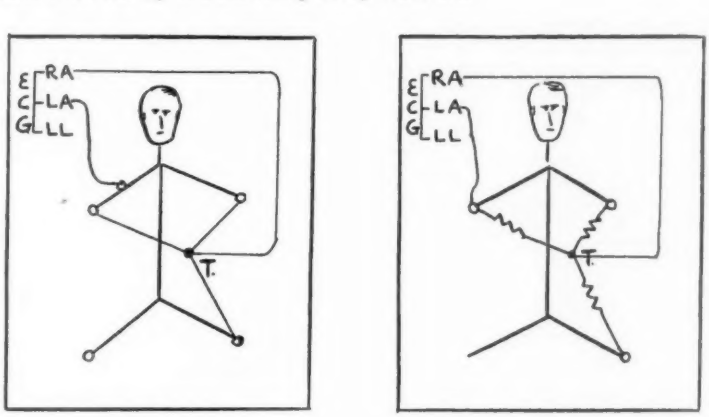


Fig. 4.—*A*, The author's indifferent electrode, connected to take the ordinary right arm lead, *Vr*. (A fourth electrode is placed on the right arm.) *B*, Wilson's indifferent electrode, connected to take the ordinary right arm lead, *Vr*.

B. Ordinary Unipolar Extremity Leads

Ordinary Right Arm Lead (Vr).—(1) Set the switch for Lead I. (2) Place the electrodes on the right and left forearms and the left leg. (3) Place a fourth electrode on the patient's right arm near the elbow. (4) Attach the indifferent electrode as for precordial leads (Fig. 4*A*). (5) Attach the *RA* lead wire to the central terminal. (6) Attach the *LA* lead wire to the fourth electrode on right arm near the elbow. (7) Standardize as usual. In the finished record, positivity will be represented by an upward deflection.

To take the ordinary left arm lead (*Vl*), attach the fourth electrode near the left elbow and proceed as above.

To record the ordinary left leg lead *(Vf)*, attach the fourth electrode near the left knee, and proceed as above.

With this technique, the records are similar to those obtained and described by Wilson, et al.,[13] and Kossmann, et al.[4]

DISCUSSION

In order to understand the operation of the author's indifferent electrode, the following presentation of the electrical principles underlying the use of an indifferent electrode of this type is necessary.

When the extremities are joined, as in Fig. 2, to record precordial potentials, the current flow, I, through the circuit may be determined by Kirchhoff's law, namely, that the total current flowing out of a central point is equal to the total current flowing into it. Thus, if the current flow at a given instant is as indicated by the arrows in Fig. 2*B*,

$$(1) \qquad I_1 = I_2 + I_3$$

$$\text{or} \qquad \frac{E_{RA} - E_T}{R_1} = \frac{E_T - E_{LA}}{R_2} + \frac{E_T - E_{LL}}{R_3}$$

If the resistances are equal, the potential at the central point, T, is equal to the mean potential of the extremities to which it is joined. The proof of this is as follows. Since the resistances are considered equal,* equation (1) may be rewritten

$$RA - T = T - LA + T - LL$$

$$\text{or} \qquad 3T = RA + LA + LL$$

$$T = \frac{RA + LA + LL}{3}$$

Since it has been demonstrated[1] that the sum of the extremity potentials equals zero (i.e., RA + LA + LL = O),

$$T = O$$

On study of this problem, we felt that the introduction of external resistances might not be necessary in view of the fairly high skin-electrode resistances, and experiments were conducted along these lines, using ordinary (No. 18) electric wire to connect the extremities (Fig. 1). The results were very satisfactory.

Carrying the theoretical analysis further, as was pointed out above, Wilson employed the fixed external resistances in order to equalize the inequalities of skin resistance. However, it must be realized that, although with this technique the differences between the total resistances become proportionately less, they still are not equal. A major objection to our technique, however, might be that the use of low-resistance wires joining the extremities (through the central terminal) would effect a decrease in the potentials at the extremities, and a marked alteration in the electrical field around the heart. In order to ascertain whether this was so, we studied the effects of shunts (connecting the extremities) on the configuration of standard leads, in the following way. The subject was a 58-year-old woman who had suffered an attack of myocardial infarction five weeks previously.

*It was to approach this condition, and thus obviate the effects of the inequalities of skin-electrode resistances,† that Wilson, et al.,[3] placed fixed resistances of 5,000 ohms between each extremity and the central terminal.

†It would be more correct to say "resistance from the electrode to the source of potential."

Experiment 1.—(1) Lead II was taken in the usual way, with electrodes on the volar surface of the right wrist and the lateral aspect of the left leg, just above the ankle (Fig. 5*A*). (2) Two additional electrodes were placed on extremities, one on the volar aspect of the right arm, 3 inches above the original electrode, and the other on the lateral aspect of the left leg, 4 inches above the original. Control Lead II was taken (Fig. 5*B*). (3) Low-resistance (No. 18) wire was connected to the electrode on the left arm and the proximal electrodes on the right arm and left leg (the author's indifferent electrode was used). Lead II was taken (Fig. 5*C*). (4) The Wilson assembly was connected (as a control) as in No. 3; Lead II was taken (Fig. 5*D*).

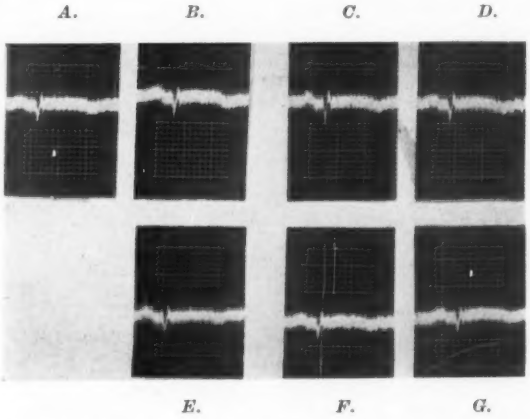


Fig. 5.—*A*, Lead II, taken with electrodes on the volar surface of the right wrist and the lateral aspect of the left leg just above the ankle. *B*, Control Lead II, after the additional electrode was placed on the volar aspect of the right arm, 3 inches above the original, and on the lateral aspect of the left leg, 4 inches above the original. *C*, Lead II after a low-resistance shunt was connected to the proximal electrodes of the right arm and left leg. *D*, Lead II after a Wilson assembly was connected to the proximal electrodes of the right arm and left leg. *E*, Lead II, taken with four electrodes on the right arm and left leg, connections being made with the proximal electrodes. *F*, Lead II after a low-resistance shunt was connected to the distal electrodes of the right arm and left leg. *G*, Lead II after a Wilson assembly was connected to the distal electrodes of the right arm and left leg.

Experiment 2.—(1) With the four electrodes on the right arm and left leg, the connection for Lead II was made with the proximal electrodes; control Lead II was taken (Fig. 5*E*). (2) Low-resistance shunts were connected to the distal electrodes on the right arm and left leg, and to the left arm; Lead II was taken (Fig. 5*F*). (3) The Wilson assembly was connected as in step 2 (for control); Lead II was taken (Fig. 5*G*).

RESULTS

Since the limbs are considered as linear extensions of points at the apices of an equilateral triangle inscribed in a spherical volume conductor,[5] a decrease of potential at any point on the extremity should be reflected along the extremity, especially at points distal to the region where the potential has been decreased. The above experiments showed absolutely no demonstrable change in the configuration of Lead II when the extremities were shunted with low-resistance wire. The reason for this is that the usual skin-electrode resistance is sufficiently high to prevent a marked drop in potential when the extremities are joined, even

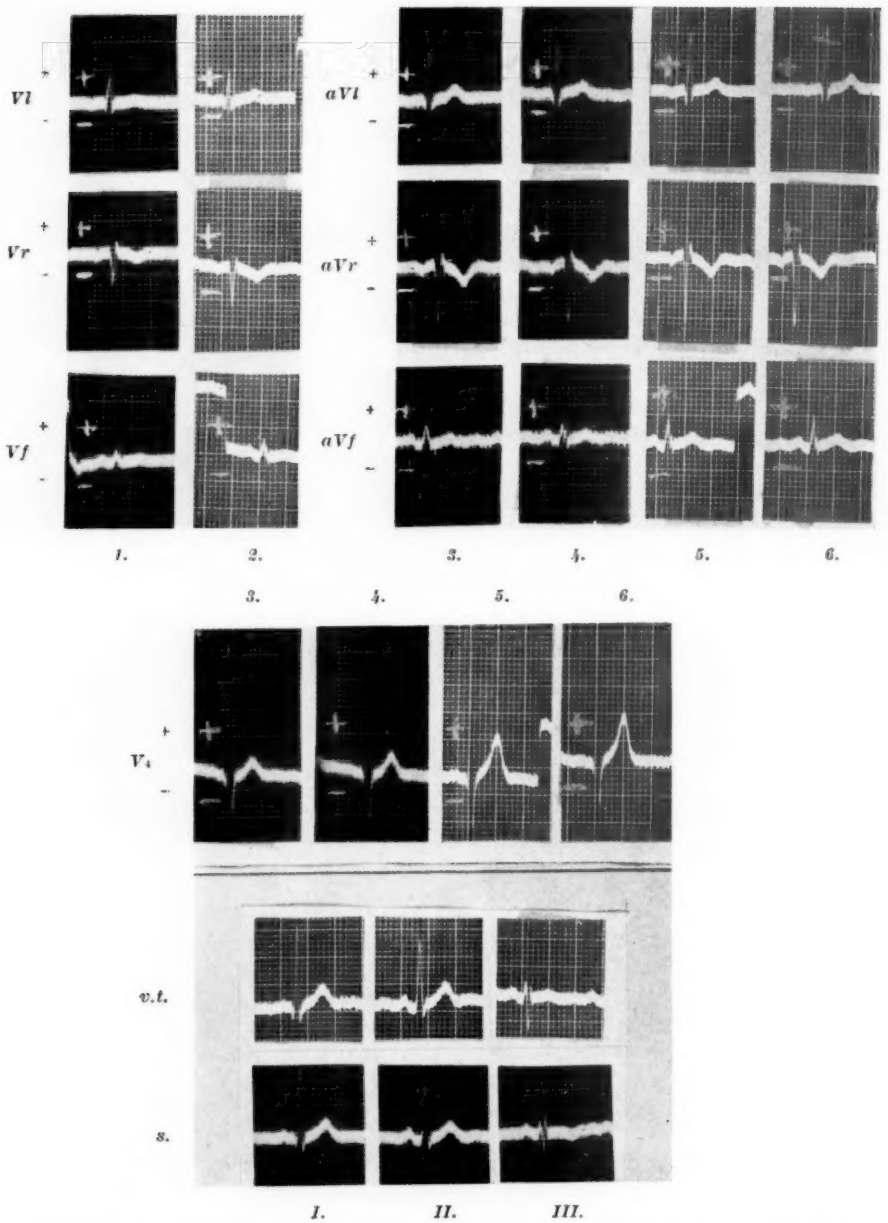


Fig. 6.—Comparison of unipolar extremity, and precordial leads taken with different techniques. Subject ♂ 28, normal. *Vl*, ordinary left arm lead; *Vr*, ordinary right arm lead; *Vf*, ordinary left leg lead; *aVl*, the *aVl* lead (the augmented left arm lead); *aVr*, the *aVr* lead (the augmented right arm lead); *aVf*, the *aVf* lead (the augmented left leg lead); V_4, precordial lead, with electrode at 5 i.c.s., mid-clavicular line; *v.t.*, standard leads taken with vacuum tube type of electrocardiograph; *s.*, standard leads taken with string galvanometer electrocardiograph; *1*, ordinary unipolar extremity leads taken with string electrocardiograph and Wilson assembly; *2*, ordinary unipolar extremity leads taken with vacuum tube electrocardiograph and Wilson assembly; *3*, augmented extremity, and precordial, leads taken with a string electrocardiograph and Wilson assembly; *4*, augmented extremity, and precordial, leads taken with a string electrocardiograph and the author's indifferent electrode; *5*, augmented extremity, and precordial, leads taken with vacuum tube electrocardiogram and the author's indifferent electrode; *6*, augmented extremity, and precordial, leads taken with vacuum tube electrocardiograph and the Wilson assembly.

through a low-resistance circuit. However, this is not to deny that there is a current flow of magnitude through the low-resistance wire, because, if it were to be connected directly to the two electrodes taking the standard lead, no deflection of the string could be obtained. (This is the reason for using a fourth electrode when ordinary unipolar extremity leads are taken.)

We have used the author's indifferent electrode in more than 1,500 cases; and in approximately 100 of these we also made not only precordial, but the unipolar extremity, leads with the Wilson assembly for comparison. This latter series comprised normal subjects and patients with abnormal auricular patterns, myocardial infarction with both Q_1 and Q_3 patterns, bundle branch block and interventricular conduction disturbances, and digitalis effects.

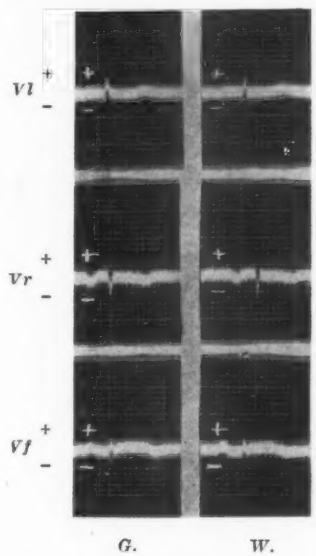


Fig. 7.—Comparison of ordinary unipolar extremity leads taken with the author's and with Wilson's indifferent electrode. *G*, Leads taken with the author's indifferent electrode; *W*, leads taken with the Wilson assembly.

Fig. 6 shows precordial Lead V_4 from a normal subject, taken with the author's indifferent electrode, with the Wilson assembly, and with a string, and a vacuum tube, type of electrocardiograph.

To conclude, for purposes of clinical electrocardiography, precordial leads taken with the author's or Wilson's indifferent electrode, using a string or a vacuum tube electrocardiograph, may be considered identical. When ordinary unipolar extremity leads are taken with the author's indifferent electrode, a fourth electrode must be placed on the extremity from which the record is being recorded, for reasons explained above. Fig. 7 shows the ordinary unipolar extremity leads, taken with the author's and Wilson's indifferent electrodes, in a case of myocardial infarction.

THE USE OF AN INDIFFERENT ELECTRODE TO OBTAIN "AUGMENTED" UNIPOLAR EXTREMITY LEADS

Realizing that extremity leads, as ordinarily taken, are of small amplitude, we devised the technique described above in order to augment the amplitude of the unipolar extremity leads. *The technique,*

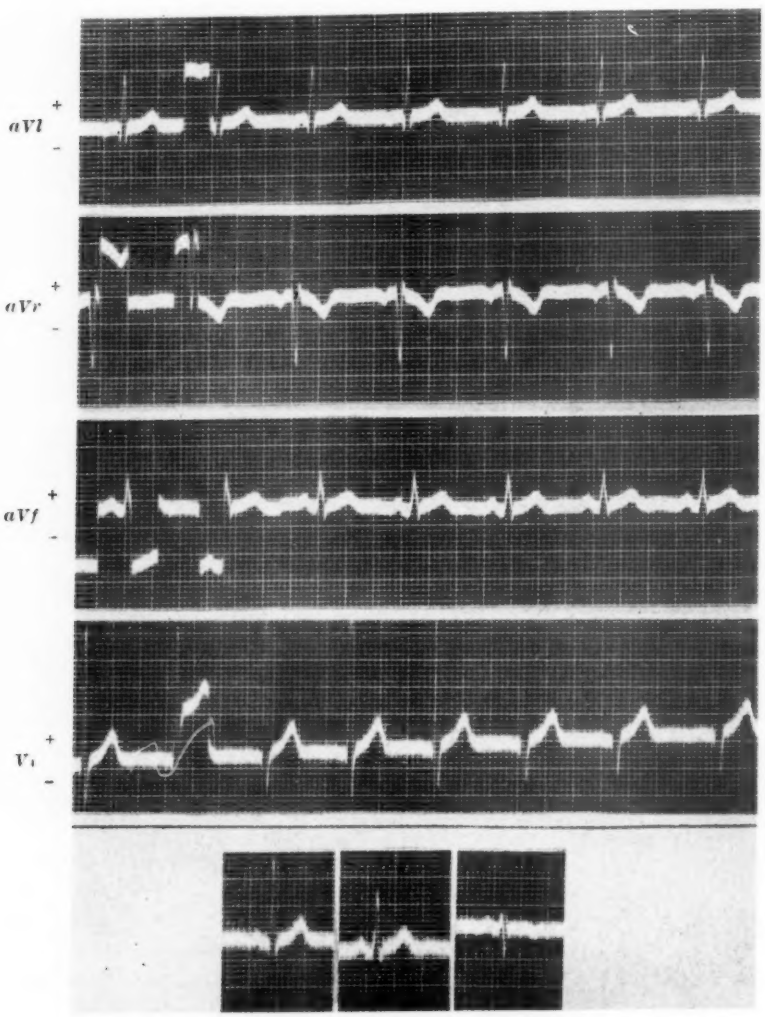


Fig. 8.—Subject ♂ 29, normal.

in essence, is that the indifferent electrode is kept off the extremity from which the record is being recorded. The proof of the validity of our technique is as follows. If the augmented right arm lead is being taken (Fig. 3), the potential at the central terminal, *T,* is equal to

$$\frac{LA + LL}{2} \text{ or } \frac{-RA}{2}$$

$$\text{Since } RA + LA + LL = 0$$
$$LA + LL = -RA$$
$$\text{and } \frac{LA + LL}{2} = \frac{-RA}{2}$$

The record so obtained would be equivalent to $RA - (\frac{-RA}{2})$ or $\frac{3}{2}$ RA.

It is for this reason that we have called the unipolar extremity records obtained with this technique augmented unipolar extremity leads. The augmented left arm and left leg leads may be similarly analyzed.

It may be pointed out that the augmented left leg potential is approximately equal to E sin α, where α is the angle made by the electrical axis with that side of Einthoven's triangle which corresponds to Lead I and E is the manifest potential. This is so because the potential of the unaugmented left leg lead equals $\frac{E \sin \alpha}{\sqrt{3}}$ ($\sqrt{3} = 1.73$ approx.).[6] As was mentioned above, just as for the precordial leads, we compared augmented unipolar extremity leads taken with the author's and Wilson's indifferent electrodes in a similar series of cases, and obtained identical results. Fig. 6 illustrates this in a normal subject.

To the augmented unipolar lead derived from the right arm we have given the name, the aVr lead. The term aVl lead indicates the augmented left arm lead. The augmented left leg lead is known as the aVf lead.* This distinguishes them from the ordinary unipolar extremity leads which are known as Vr, Vl, and Vf, respectively.[3]

CONCLUSIONS

When precordial leads are being recorded, the use of an indifferent electrode of the type described above is predicated on the concept that, when the extremities are connected to a central terminal, the potential at this central point equals zero. Theoretically, this holds only when all resistances are equal. However, for purposes of clinical electrocardiography, it is not necessary to equalize the resistances of the circuit by the introduction of fixed resistances (the Wilson assembly); the three extremities may be joined to a central terminal with ordinary electric wire, and the Wilson assembly and the author's indifferent electrode may be used interchangeably in the recording of precordial leads.

When ordinary unipolar extremity leads are being recorded with the author's indifferent electrode, a technique slightly different from that used with the Wilson indifferent electrode must be employed (Fig. 4).

*The characteristics of these leads in both normal and abnormal subjects will be presented elsewhere.[7] Fig. 8, from our records, illustrates how we file these leads.

However, we have, in our studies of unipolar extremity potentials, discarded the ordinary unipolar extremity leads and use a technique in which augmented unipolar extremity leads are obtained. Essentially, our technique consists in *not* connecting the extremity from which the electrocardiogram is being recorded to the central terminal; the other two extremities are so connected. It is immaterial whether the author's or Wilson's indifferent electrode is used, with either a string or vacuum tube electrocardiograph. We have designated the augmented unipolar extremity leads obtained with our technique as follows: (1) the aVr lead, which records potentials from the right upper extremity; (2) the aVl lead, which records potentials from the left upper extremity; (3) the aVf lead, which records potentials from the left lower extremity.

SUMMARY

1. The construction of a simple indifferent electrode of zero potential is described.

2. Theoretical and experimental evidence of its efficiency is presented.

3. A technique for obtaining augmented unipolar extremity leads is described.

The author wishes to thank Dr. Frank N. Wilson, of Ann Arbor, Mich., for his helpful suggestions in the preparation of the manuscript, and Dr. Samuel Alpert, of New York, who took several of the electrocardiograms used in this study.

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1100 GRAND CONCOURSE

LUMBAR SYMPATHECTOMY IN THE TREATMENT OF PERIPHERAL ARTERIOSCLEROTIC DISEASE

II. Gangrene Following Operation in Improperly Selected Cases

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IN A RECENT communication[1] criteria were presented for the selection of cases of peripheral arteriosclerotic disease in which lumbar sympathectomy is indicated, together with a résumé of the results obtained in a group of twelve such patients who had been observed for a period of a year, or longer, after operation. This original series has now been extended to include twenty-eight arteriosclerotic lower extremities in which sympathectomy was considered advisable. The results obtained in the entire group have been uniformly encouraging. It will be recalled that this group was a highly selected one and included only those cases in which preoperative examination revealed the presence of a healthy collateral arterial circulation and a flexible peripheral arteriolar bed, but in which sympathetic constrictor impulses to the latter frustrated all attempts at conservative vasodilating therapy.

The necessity of being circumspect in the selection of cases of peripheral arteriosclerotic disease for lumbar sympathectomy cannot be overemphasized. The suggested criteria must be strictly adhered to, lest not only disappointing, but, in some instances, disastrous, results ensue. It has been personally observed that, in a certain type of arteriosclerotic extremity, sympathetic denervation of the foot is followed by gangrene. Preoperative clinical observation indicates that this untoward result is likely to follow when the disease process, by virtue of its location or its extent, has blocked or obliterated the collateral circulation. In such instances the nutrition of the foot is precariously maintained by the seepage of blood through partially occluded, diseased channels which can neither dilate nor hypertrophy in response to a surgically induced reduction of peripheral resistance to blood flow. A rapid onset of gangrene after lumbar sympathectomy has been personally encountered on three occasions. Despite the absence of an effective collateral circulation, the distal arteriolar beds remained flexible, as was indicated by a measurable rise in the surface temperature of all three feet, after sympathectomy, to vasodilatation levels 2° to 5° C. higher than were anticipated from preoperative studies. However, for reasons which will shortly become

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apparent, this rise in skin temperature was deceptive. In these cases there were other definite and readily recognized characteristics. Oscillometric readings at the supramalleolar level were zero in all three. Extreme pallor of the foot on elevation, with rubor or cyanosis on dependency, was present in all three. Conspicuous atrophy of the skin and subcutaneous tissue was observed in two. Finally, the filling time of the emptied dorsal venous arches was prolonged well beyond thirty seconds in all three feet.[2]

The mechanism whereby lumbar sympathectomy apparently expedited tissue necrosis in these cases is somewhat obscure. It cannot be accounted for by sudden thrombosis of a previously patent major vessel for several reasons. (1) The only major artery in which a pulsation could be felt preoperatively in any of these extremities was the femoral; pulsation in the femoral, when it was present preoperatively, remained undiminished until the time of amputation. (2) The onset of gangrene was not acute, and its development was slowly progressive. (3) The gangrene was patchy in its distribution, and the intervening tissue remained healthy until the time of amputation. (4) Except for one case in which the femoral and popliteal arteries had become acutely thrombosed preceding the sympathectomy, pathologic examination of the arteries did not reveal evidence of a recent thrombosis.

A consideration of the part played by the arteriovenous anastomoses in the presence of serious obstruction to the flow of blood to the foot may illuminate the problem. Popoff[3] suggested, and Harpuder and his co-workers[4] presented experimental evidence, that, in the presence of peripheral vascular disease, the arteriovenous anastomoses which are distributed throughout the foot may shunt a significant quantity of blood directly into the venous circulation before it has the opportunity of reaching the capillary bed, where it would be available for cellular nutrition. In the light of this evidence, it is not inconceivable that, in the presence of a rigidly impaired blood supply, surgically induced relaxation of patent and flexible arteriovenous anastomoses in an ischemic foot could shunt blood from the capillary beds in sufficient quantity to cause tissue necrosis and gangrene. Since surface temperature is apparently controlled by the volume rate of blood flow through these arteriovenous shunts, an explanation is thus available for the fact that a foot may become warm and also gangrenous as a direct result of sympathectomy.

CASE REPORTS

CASE 1.—A 61-year-old white man gave a history of intolerable, constant pain in his right foot, accompanied by subjective sensations of coldness. Intermittent claudication on the slightest exertion was likewise present. The symptoms had begun three years previously and had progressively increased in severity.

Examination.—Oscillometric examination revealed absence of pulsation in the lower part of the leg. A pulsation was palpable in the femoral, but not in the popliteal, posterior tibial, or dorsalis pedis arteries. The venous filling time was sixty seconds. There was extreme pallor of the foot on elevation, with cyanosis and rubor on dependency. The skin of the foot was very cold to the touch and was atrophic; neither ulceration nor gangrene was present. Immersion of the foot in a whirlpool bath at a temperature of 95° F. produced intense cyanosis and an increase in the pain.

Lumbar sympathectomy was performed in an attempt to relieve the pain. Within twenty-four hours the foot became palpably warm, but the pain was not relieved. Within two weeks the foot began to show patchy areas of necrosis. During the ensuing four months these gangrenous patches increased in size and coalesced, and, finally, a thigh amputation was deemed necessary. Pathologic examination of the amputated specimen revealed that the popliteal, posterior tibial, and anterior tibial arteries were completely obstructed by a chronic arteriosclerotic process.

CASE 2.—A white man, aged 63 years, gave a history of intermittent claudication of fifteen months' duration in his left leg. One week before admission he experienced sudden numbness and weakness in the foot.

Examination.—The pain was so severe that large doses of analgesics were required. Oscillometric examination revealed absence of pulsation in the lower part of the leg. A pulsation was palpable in the femoral artery, but none could be felt in the popliteal, posterior tibial, or dorsalis pedis arteries. The foot was very cold to the touch, cyanotic, and sweaty. There was extreme pallor of the foot on elevation. There was no ulceration or gangrene. The venous filling time was fifty seconds. A diagnosis of acute thrombosis of an arteriosclerotic popliteal artery was made, and lumbar sympathectomy was performed for the relief of the vasospasm and the intractable pain. Within twenty-four hours the foot became very warm. However, one week after operation the second and third toes began to turn dark and soon became completely gangrenous. Later, a large patch of painful, ischemic necrosis appeared on the dorsum of the foot. The rest of the foot remained warm, but the painful gangrenous parts failed to demarcate, and, two months after the sympathectomy, it was necessary to perform a low thigh amputation. Pathologic examination of the amputated specimen showed that the terminal portion of the femoral and the popliteal arteries was involved by a severe arteriosclerotic process and occluded by an organizing thrombus.

CASE 3.—A 63-year-old white man gave a history that twelve months previously he began to experience burning pain in his right foot; this was accompanied by sensations of coldness and numbness, and by paresthesias. Intermittent claudication was also present. During the preceding year the pain in the foot had progressed to the point where it was intolerable.

Examination.—There was extreme pallor of the foot on elevation, with rubor on dependency. Oscillometric examination revealed no pulsation in the lower part of the leg. No pulsation was palpable in the femoral, posterior tibial, dorsalis pedis, or popliteal arteries. The venous filling time was sixty seconds. There was marked atrophy of the skin and subcutaneous tissues of the foot and toes. Neither ulceration nor gangrene was present.

Lumbar sympathectomy was done in an attempt to relieve the intense pain. Within twenty-four hours the foot became very warm to the touch, but the pain was not relieved. One week later an ulcer suddenly appeared on the dorsum of the fifth toe. It refused to heal and became gangrenous. The entire toe then became gangrenous, and the gangrene extended into the foot. During the following four months several patches of gangrene appeared on the dorsum of the foot, and two

large areas of gangrene developed on the inner side of the lower and medial portions of the leg. A thigh amputation was performed. Pathologic examination of the amputated specimen showed total obliteration of the femoral and popliteal arteries by a chronic arteriosclerotic process.

DISCUSSION

It is quite evident that one cannot rely too much on surface temperature studies in evaluating the nutritive efficiency of the circulation through an arteriosclerotic foot. In Cases 2 and 3 the skin temperatures of the sympathectomized feet and lower portions of the legs rose to levels in excess of 30° C. as a result of surgically induced relaxation of the distal arteriolar beds, but they became gangrenous after sympathectomy, and probably as a direct result thereof.

Therefore, in evaluating the vascular efficiency of an arteriosclerotic extremity, the important consideration is whether any therapeutic attempt to produce peripheral vasodilatation will actually increase the flow of blood through the capillary bed, where it can do some good; and the important factor in such an evaluation revolves about the presence or absence of an adequate collateral circulation. Unless an effective collateral circulation is present, blood will not reach the foot in sufficient quantity to more than compensate for that which is shunted away from the capillary bed as a result of the therapeutically induced relaxation of the arteriovenous anastomoses. Under such circumstances, vasodilating methods may do more harm than good.

The value of instrumental procedures in gauging collateral circulation is limited. An effective collateral circulation may be present even when arterial pulsations, as measured by the oscillometer, are absent. A *rapid* rise in the distal skin temperatures to vasodilatation levels of at least 30° C. after a diagnostically induced relaxation of the peripheral arterioles, with concomitant fading of cyanosis, indicates the presence of an adequate collateral circulation. However, failure to obtain such a favorable response may be merely the result of an unusually persistent degree of vasoconstrictor tone or of faulty technique. On the other hand, if the arteriovenous anastomoses are flexible, a slow rise in the distal skin temperatures may follow sympathectomy in the presence of a greatly impaired collateral circulation.

Therefore, it may become necessary to base one's evaluation chiefly on clinical observations. A combination of constant, severe pain in the foot, extreme pallor of the foot on elevation, cyanosis and rubor on dependency, atrophy of the skin and its appendages, thinning, with a loss of elasticity, of subcutaneous tissue, significantly delayed filling of the emptied dorsal venous arch, and an increase in pain and cyanosis on immersing the foot in warm water can be accepted as evidence of advanced involvement of the collateral circulation by the obliterating

process. Absence of this combination indicates that there is an open and healthy circulation, and only in such cases should lumbar sympathectomy be performed.

Even if it is otherwise indicated, sympathetic denervation of an arteriosclerotic leg and foot should be avoided when symptoms or an exacerbation of symptoms are of recent origin. In such instances the diminution in peripheral blood flow and the increase in blood coagulability which follow operation may accelerate the spread of a fresh thrombotic process. When one is in doubt as to the activity of a thrombotic process, it is best to postpone operation for a period of six months, during which time the patient can be treated conservatively.

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ANGINA PECTORIS

Significant Electrocardiographic Changes Following Exercise

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THE diagnosis of angina pectoris today rests essentially upon the patient's symptoms and upon the interpretation of these symptoms by the physician. Frequently the diagnosis is difficult to establish because the symptoms are atypical and bizarre and because indefinite pain in the chest occurs in cardiac diseases other than angina pectoris. The establishment of objective evidence would be of inestimable value in consideration of the grave prognosis in angina pectoris, of its increasing frequency, especially in the earlier decades of life, and, in approximately 25 per cent of the cases, of the negative results of physical, roentgenologic, and routine electrocardiographic examination.[1]

According to the present concept, angina pectoris is caused by transient coronary insufficiency, i.e., a relative disproportion at a given moment between the coronary blood flow and the work of the heart. Coronary disease is, of course, the predominant underlying lesion. But many other conditions, such as aortic valvular disease, thyrotoxicosis, anemia, and paroxysmal arrhythmia, may also unmask latent coronary disease and produce angina pectoris.

In the search for objective criteria, electrocardiographic studies have been made during induced attacks of coronary insufficiency. For various reasons (such as small number of patients, inadequate controls, infrequent use of the chest lead), no general agreement has been reached as to the value of the methods used. We have reinvestigated the problem by inducing coronary insufficiency with a standard exercise test and by taking four-lead electrocardiograms during the induced attack.

Various methods have been used to induce coronary insufficiency. Levine, et al.,[2] first suggested adrenalin, but the lack of control over the parenterally injected drug, the unpleasant subjective reaction even in normal persons, and the danger of producing a severe attack militated against its use. Greene and Gilbert[3] first studied the effect of rebreathing on the electrocardiogram in normal persons, and Rothschild and Kissin[4-6] were the first to apply this test to patients with angina pectoris. They noted S-T depression in controls and in cardiac patients with and

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without angina. The degree of deviation was related to the degree of anoxemia. By the same technique, Katz, Hamburger, and Schultz[7] studied normal persons and patients with angina pectoris. In both groups, depression of the S-T segment, as well as flattening and inversion of the T waves, occurred. They concluded that some factor in addition to anoxemia is concerned in the production of anginal pain and that this variable makes it impossible to predict accurately whether or not induced anoxemia will cause pain. They discouraged the use of anoxemia because of its variable results and hazards. Levy, et al.,[8, 9] studied the effects of inhaling a 10 per cent oxygen mixture on a large group of normal persons and seventeen patients with definite angina, as well as a group of 115 normal persons and 147 patients with suspected or manifest cardiac disease caused by coronary sclerosis or hypertension. As a result of this study they set up definite criteria for abnormal responses. A few of the patients in the latter group had vasovagal reactions, convulsive seizures, and mental confusion during the test; however, none of these reactions was serious. Positive tests were obtained in 55 per cent of seventy-three patients with coronary sclerosis and a history of anginal attacks. Because of the disadvantages previously mentioned, as well as the danger of pulmonary edema, the necessity of insuring accurate concentrations of oxygen, and the elaborate equipment required, the use of this method of producing cardiac anoxemia and angina pectoris will be limited.

For many years, transient electrocardiographic changes have been recorded during spontaneous attacks of angina; the most common are S-T deviation and T-wave changes. The electrocardiographic changes which we have observed during spontaneous and induced attacks of angina are like those of Shapiro and Smyth[10] and Wood and Wolferth.[11]

Wood and Wolferth[11] made standard three-lead electrocardiograms before and after exercise in a study of 162 controls, including cardiac patients without angina, patients with noncardiac pain, and twenty-four patients with angina. None of the controls showed S-T displacement or inversion of the T wave, but one-half of the patients with angina developed these changes after exercise. Chest leads were not employed. Missal[12] reported that in forty normal persons no S-T displacement of more than 1.0 mm. and no reversal of the T wave from its original direction took place after exercise. In forty cases of angina his significant observations were: depression of the S-T segment, inversion of T waves, and temporary disappearance of the Q wave in the chest lead. Lead IV was used in only three cases. Siegel and Feil[13] reported eleven cases of transient anginal attacks, some spontaneous and some precipitated by exercise, in eight of which inversion of the T wave and/or depression of the S-T segment occurred. These changes disappeared after cessation of the pain. Electrocardiograms which were taken during the pains of labor and renal colic revealed no T-wave or S-T changes.

Katz and Landt[14] studied the four-lead electrocardiogram after exercise in twenty cases of angina pectoris; they mentioned no controls. In the standard three leads they noted a shift in axis, changes in T waves opposite to the direction of the QRS, and S-T displacement. In the chest lead they found S-T elevation and T-wave changes. Riseman, et al.,[15] in a recent article, which included a comprehensive review of the literature, reported that they studied twenty patients with angina pectoris (no controls) by taking continuous electrocardiograms and recording only one lead a day before, during, and after exercise over the two-step stairs to the point of pain. S-T deviation was the most common change; nineteen of seventy-six leads showed a change of 1.5 to 3.0 millivolts. Since most of these changes occurred in the chest lead, they studied this lead alone in fifteen controls and fifteen anginal patients after twenty complete trips over the two-step stairs. Only two of the anginal patients experienced pain. In the control group no S-T deviation greater than 1.0 mm. occurred, and the T wave decreased from 2 to 7 mm. in thirteen instances. In eleven of the patients with angina pectoris, deviation of the S-T segment of 1 to 2 mm. was noted, and, in two, of more than 2 mm. The T wave decreased 2 to 7 mm. in four patients and increased 2 to 4 mm. in five patients.

Evans and Bourne[16] took four-lead electrocardiograms on ten controls and twenty patients with angina pectoris whom they submitted to both the anoxemia and the exercise tests. No S-T segment changes or T-wave inversion was noted in the controls, but minor changes occurred in the T-wave voltage. Eleven of the patients with angina showed no changes, and nine showed some changes after anoxemia or exercise. After exercise, diphasic or inverted T waves and variations in the S-T segment, from slight to 2.0 mm., were noted. These authors concluded that the exercise test apparently results in significant changes as often as, and probably more often than, the anoxemia test, and that it is much more easily performed.

Missal[12] stated that electrocardiograms of healthy athletes taken after marathon running show no S-T changes of more than 1.0 mm. Cooper, O'Sullivan, and Hughes[17] obtained electrocardiograms on athletes after strenuous rowing. The electrocardiograms illustrated in their article showed no significant S-T segment or T-wave changes, according to our criteria.

PROCEDURE

In our study the exercise test described by Master and Oppenheimer[18] was used. A control electrocardiogram was taken with the patient in the recumbent position. Then, with the electrodes still in place, he was exercised on the stairs (at room temperature) until a typical attack of pain occurred, or, lacking that, until he was tired or dyspneic. Immediately after the exercise he was again placed in the recumbent position and a second electrocardiogram was recorded. Leads IV, I, II, and III were taken in that order. In some cases the pain had ceased after the first

lead or two had been taken; in others it persisted during the entire recording. On an average, three minutes were required to take the electrocardiograms. In some instances the exercise was stopped at the first sign of angina, and, in others, it was continued until the attack was of the severity usually experienced by the patient. In no instance was the induced pain more severe than that experienced by the patient as an everyday occurrence. In some cases of known angina the pain which causes intermittent claudication prevented development of the characteristic substernal pain. No attempt was made to exercise these patients in a different manner. They were allowed to select their own pace and were urged to keep to it without slowing down or "resting." The number of round trips on the two-step stairs varied from eight to fifty; the average was about twenty (depending upon the amount of exercise necessary to produce pain). The controls were exercised at a much faster pace, but also to the point of dyspnea; the average number of round trips was twenty-five. The exercise test was performed without incident. No patient had pain that could not easily be stopped by rest and nitroglycerin. During the entire procedure a physician was in attendance, and notations on the number of trips and on the quality and quantity of pain were made.

ANALYSIS OF 100 CONTROL SUBJECTS AFTER EXERCISE

In Table I the control group is classified according to age, sex, and whether the electrocardiogram was normal or abnormal before exercise (called control electrocardiograms). Of the 100 subjects, fifty-six were males and forty-four were females; fifty-nine were over 40 years of age and thirty-six were over 50. There were seventy-two normal and twenty-eight abnormal control electrocardiograms.

TABLE I

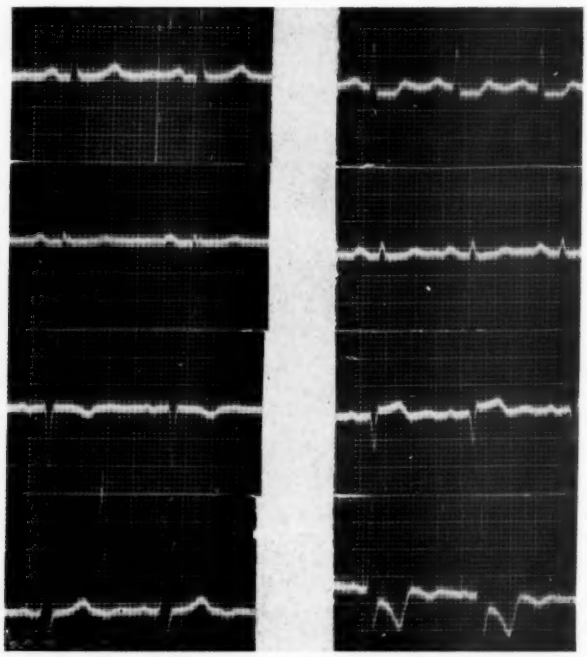
CORRELATION OF AGE, SEX, AND NORMAL OR ABNORMAL CONTROL ELECTROCARDIOGRAM IN 100 CONTROL SUBJECTS

AGE	MALE		FEMALE	
	NORMAL CONTROL EKG	ABNORMAL CONTROL EKG	NORMAL CONTROL EKG	ABNORMAL CONTROL EKG
11-20	0	0	1	1
21-30	5	1	8	3
31-40	11	3	4	4
41-50	10	1	5	7
51-60	14	5	4	2
61-70	4	0	4	0
71-80	1	1	1	0
Total	45	11	27	17

The S-T segment changes were analyzed in each lead. After exercise, no subject developed or exceeded an S-T deviation of 1.0 mm. in Lead I, 1.5 mm. in Lead II, 1.5 mm. in Lead III, or 2.0 mm. in Lead IV. There were, however, many minor segment changes that did not approach those previously mentioned. In Lead I, twenty-seven of these did not exceed 0.5 mm.; in Lead II, twenty-four did not exceed 1.0 mm.; in Lead III, four did not exceed 1.0 mm.; in Lead IV, seventeen did not exceed 1.0 mm., and two showed an S-T deviation of 1.5 mm. There were only six

instances of S-T elevation: four in Lead III not exceeding 1.0 mm., and two in Lead IV not exceeding 1.5 mm.

Many T-wave changes occurred in this group after exercise. Because of the variability of T_3, this lead was ignored. No persons with an upright T_1, T_2, or T_4 had diphasic or inverted T waves after exercise. Occasionally diphasic or inverted T waves became upright. The responses in voltage were variable; an increase or decrease in the height of the T waves was common. In the limb leads these changes usually did not exceed 2.0 mm., and, in the chest lead, 3.0 mm.; however, changes up to 4 mm. occurred in both. In five instances a previously inverted T_4 became upright after exercise.



A. *B.*

Fig. 1.—Electrocardiogram (*A*) before and (*B*) after exercise. Woman (U 51950), aged 54. Lower sternal pain with cholecystitis was considered in diagnosis. Note significant changes with exercise. S-T_1 has characteristic contour and depth.

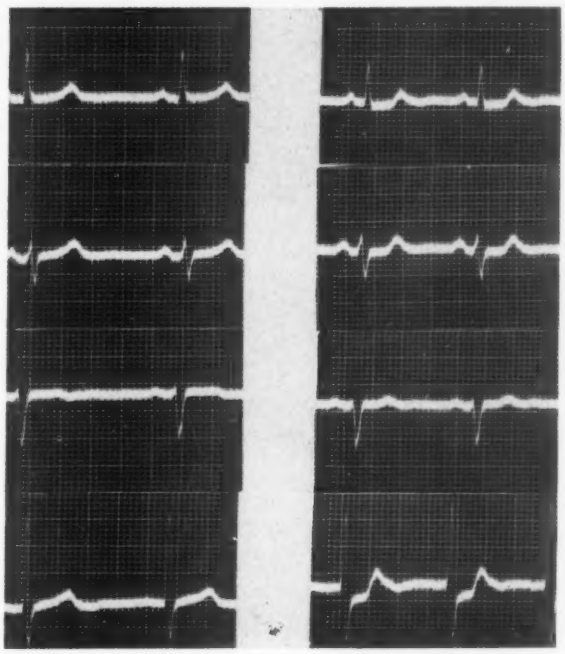
No changes in rhythm were noted, with the exception of occasional extrasystoles. Only slight axis changes and no marked P-wave variations occurred. The P-R conduction time, as well as the duration of QRS, remained within normal limits except in one case, in which a QRS of 0.10 increased to 0.12 second. The average rate increase was approximately 23 per minute.

From our study of these 100 control subjects we concluded that the abnormal electrocardiographic response to exercise consists of an S-T depression or elevation of 1.0 mm. or more in Lead I, of 1.5 mm. or

more in Lead II, of 1.5 mm. or more in Lead III, and of 2.0 mm. or more in Lead IV; or consists of a change from an upright to a diphasic or inverted T_1, T_2, or T_4. If any one of these changes is present, the curve is considered abnormal.

ANALYSIS OF THE RESPONSE OF SIXTY-SIX PATIENTS WITH ANGINA PECTORIS TO EXERCISE

Of the sixty-six patients with angina pectoris, fifty-three were males and thirteen were females, a ratio of 4:1. Fifty of these patients were over 50 years of age; twenty-five, or 38 per cent, had normal control (pre-exercise), four-lead electrocardiograms. In forty-five cases the typical pain of angina pectoris developed during the exercise test; pain was not reproduced in twenty-one. In two instances both angina and bundle branch block developed. Since the presence of bundle branch block interferes with the detailed interpretation of S-T segment and T-wave changes, these two cases will be considered separately.

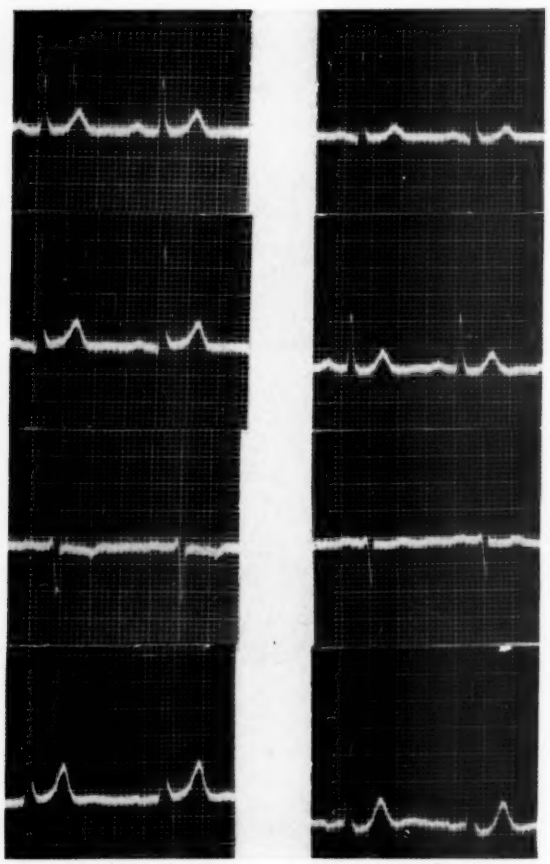


A. *B.*

Fig. 2.—Electrocardiogram (*A*) before and (*B*) after exercise. Man (U 52773), aged 68. Atypical chest pain did not permit a definite clinical diagnosis of angina pectoris. Death followed six months later from coronary occlusion.

The remaining sixty-four patients were divided into those who developed pain (forty-three) and those who did not develop pain (twenty-one) during the exercise test. Table II shows the incidence and magnitude of the S-T segment changes in the various leads and their correlation with the reproduction or nonreproduction of angina. There were

136 instances of S-T depression, and, in forty-nine of these, it reached a significant level (e.g., what was considered abnormal in comparison with the controls). There were only sixteen instances of S-T elevation, and in only six was it significant.

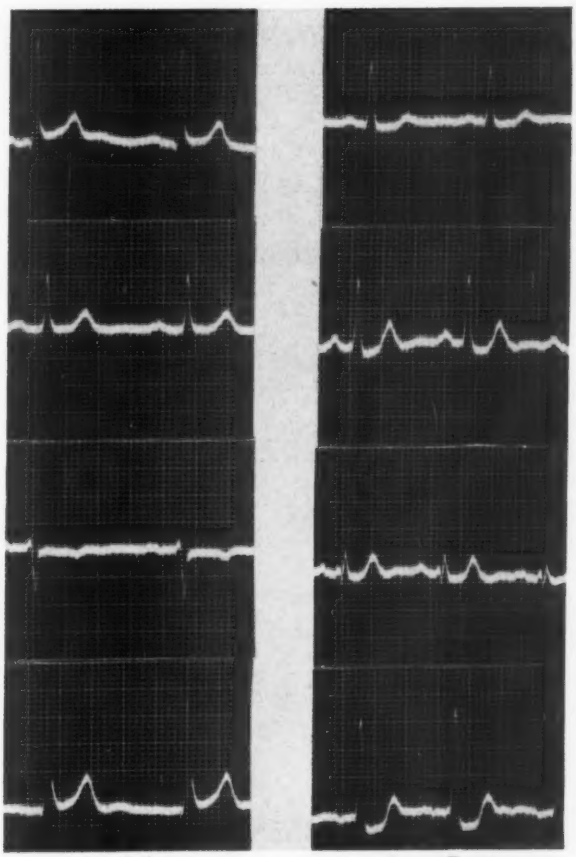


A. *B.*

Fig. 3*A* and *B*.—Electrocardiogram (*A*) before and (*B*) after mild exercise. Man (U 19319), aged 59. Changes after mild exercise and mild pain were not significant.

The distribution of significant S-T segment and T-wave changes in the various leads is shown in Table III. Of the total of fifty-five significant S-T changes, forty-nine, or 89 per cent, were found in cases in which pain was produced by the exercise test, whereas six, or 11 per cent, occurred in cases in which the test failed to reproduce angina; twenty-three, or 41 per cent, occurred in Lead IV. Of the total of twenty-six significant T-wave changes, twenty-one, or 80 per cent, were found in the patients who experienced pain on exercise, whereas six, or 20 per cent, occurred in patients who did not have pain with exercise; seven, or 27 per cent, occurred in Lead IV. Of the total of eighty-

one significant S-T segment and T-wave changes, seventy, or 86 per cent, occurred when pain was reproduced, and eleven, or 14 per cent, occurred when pain was not elicited.



C. *D.*

Fig. 3*C* and *D*.—Electrocardiogram (*C*) before and (*D*) after severe exercise. Man (U 19319), aged 59. Changes after severe exercise and pain of usual severity were considered significant.

Table IV gives the number of cases of angina pectoris (including the two patients with bundle branch block) in which significant four-lead electrocardiographic abnormalities developed after exercise; it shows whether or not the S-T segment and T-wave changes occurred separately or in combination; and it correlates these changes with the reproduction or nonreproduction of pain. It reveals the importance of eliciting an attack of typical chest pain during the exercise test. Electrocardiograms characteristic of coronary insufficiency were obtained in two-thirds of the forty-five cases in which pain was reproduced, and in only one-third of the twenty-one cases in which pain was not reproduced on exercise.

TABLE II

S-T SEGMENT CHANGES OF THE STANDARD FOUR-LEAD ELECTROCARDIOGRAM IN SIXTY-FOUR PATIENTS WITH ANGINA PECTORIS FOLLOWING EXERCISE; CORRELATION WITH REPRODUCTION (P) OR NONREPRODUCTION (NP) OF TYPICAL ANGINAL PAIN

S-T SEGMENT DEVIATION	MM.	LEAD I		LEAD II		LEAD III		LEAD IV	
		P	NP	P	NP	P	NP	P	NP
No change	0.0	13	12	15	14	16	18	5	11
Depression	0.5	14	4	10	3	13	7	6	7
	1.0	11	5	9	4	2	1	3	2
	1.5	4	0	5	0	0	0	2	0
	2.0	1	0	3	0	0	0	10	1
	2.5	0	0	0	0	0	0	6	0
	3.0	0	0	0	0	0	0	0	0
	3.5	0	0	0	0	0	0	1	0
	4.0	0	0	0	0	0	0	1	0
	4.5	0	0	0	0	0	0	1	0
Elevation	0.5	0	0	0	0	5	0	1	0
	1.0	0	0	0	0	0	0	2	0
	1.5	0	0	0	0	1	0	2	0
	2.0	0	0	1	0	1	0	2	0
	2.5	0	0	0	0	0	0	0	0
	3.0	0	0	0	0	0	0	0	0
	3.5	0	0	0	0	0	0	1	0

TABLE III

DISTRIBUTION OF SIGNIFICANT CHANGES IN THE VARIOUS LEADS IN ANGINAL PATIENTS FOLLOWING EXERCISE; CORRELATION WITH REPRODUCTION (P) OR NONREPRODUCTION (NP) OF PAIN

LEAD	SIGNIFICANT S-T SEGMENT CHANGES		SIGNIFICANT T-WAVE CHANGES	
	P	NP	P	NP
I	16	5	11	1
II	9	0	6	1
III	2	0		
IV	22	1	4	3
Total	49	6	21	5

TABLE IV

SUMMARY OF THE TYPE AND INCIDENCE OF SIGNIFICANT CHANGES IN THE FOUR-LEAD ELECTROCARDIOGRAM FOLLOWING EXERCISE IN SIXTY-SIX PATIENTS WITH ANGINA PECTORIS (INCLUDING TWO PATIENTS WITH BUNDLE BRANCH BLOCK); CORRELATION WITH REPRODUCTION OR NONREPRODUCTION OF PAIN

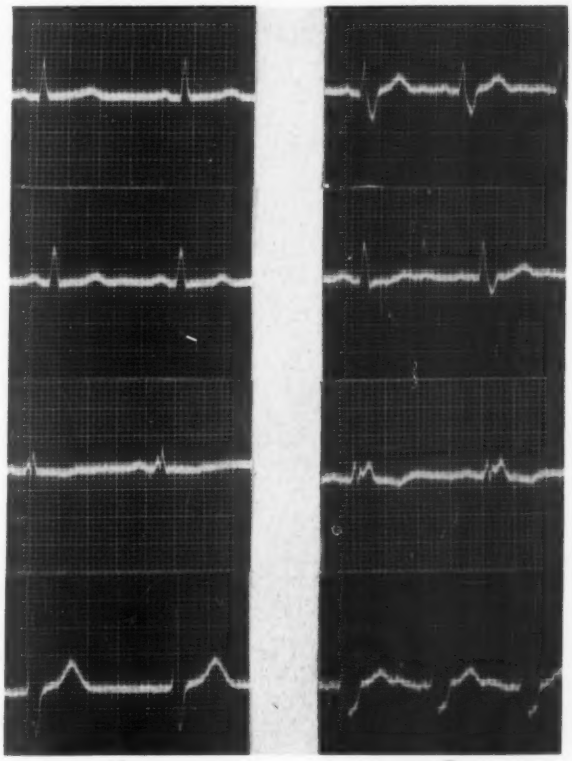
	NO. OF PATIENTS	SIGNIFICANT CHANGES					
		S-T SEGMENT (ALONE)	T WAVE (ALONE)	S-T SEGMENT AND T WAVE (COMBINATION)	BUNDLE BRANCH BLOCK	TOTAL	PER CENT
Pain	45	15	1	12	2	30	66⅔
No pain	21	2	2	3	0	7	33⅓
Total	66	17	3	15	2	37	56

Irrespective of the presence or absence of pain during the test, 56 per cent of the total of sixty-six patients had significant electrocardiographic changes after exercise.

TABLE V

RELATIVE IMPORTANCE OF STANDARD AND CHEST LEADS IN THIRTY-SEVEN PATIENTS WITH SIGNIFICANT ELECTROCARDIOGRAPHIC CHANGES AFTER EXERCISE (INCLUDING TWO PATIENTS WITH BUNDLE BRANCH BLOCK)

LEADS	SIGNIFICANT CHANGES	
	NO. OF PATIENTS	PER CENT
Standard leads alone	12	32½
Chest lead alone	8	21½
Standard leads and chest lead combined	17	46



A. *B.*

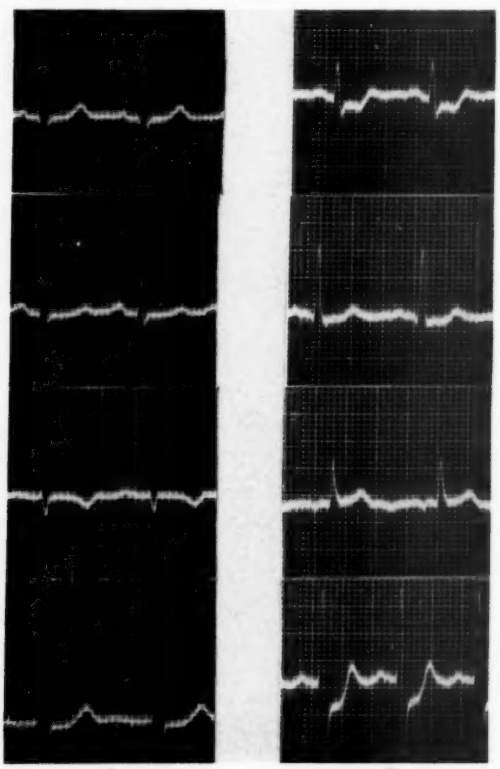
Fig. 4.—Electrocardiogram (*A*) before and (*B*) after exercise. Man, aged 45. Note bundle branch block after exercise.

Table V shows the relative importance of the standard leads and the chest lead. The chest lead was abnormal in twenty-five of the thirty-seven patients (67 per cent) with significant electrocardiographic changes; in eight patients (21.5 per cent) it showed the only significant change which was noted in the four-lead electrocardiogram.

Figs. 1 to 7 illustrate typical electrocardiographic changes after exercise.

DISCUSSION

A study of the control (nonangina) group reveals that in the four-lead electrocardiogram there were seventy-three instances of S-T deviation. In cases of angina, the development of S-T changes alone after exercise cannot be considered important unless they reach a certain magnitude. Of 152 S-T segment changes in the cases of angina pectoris,

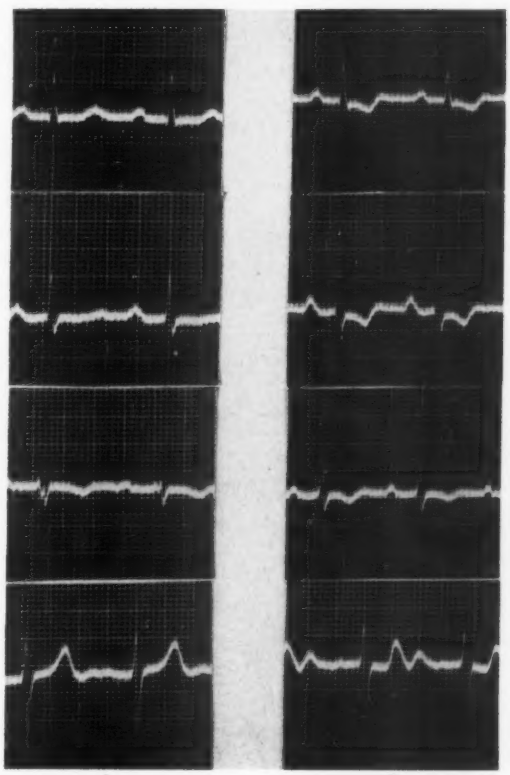


A. *B.*

Fig. 5.—Electrocardiogram (*A*) before and (*B*) after exercise. Man, aged 60. Note T-wave and S-T segment changes. Pain was produced by exercise.

only fifty-five were significant (elevation or depression). The infrequency of elevation should be noted. Only in rare instances were the changes reciprocal. The contour of the S-T segment was variable; there was either a smooth, rounded type of depression, or a very rapid depression, with flattening of the main portion of the segment, followed by a quick return to the isoelectric line, such as is found in certain types of coronary arterial disease. The latter type of contour, as illustrated in Fig. 1 ($S\text{-}T_1$, after exercise), is very important. Many of the patients with angina pectoris showed this characteristic change in contour, although the degree of the S-T depression was not abnormal. We did not use this contour change as a criterion for a positive test because it is sub-

ject to individual interpretation, and, unlike the depth of the S-T segment deviation, cannot be measured accurately. However, if this characteristic contour of the S-T segment is found, coronary insufficiency may be present regardless of the depth of the S-T deviation. Future observations will determine the importance of the "significant contour" without significant deviation of the S-T segment.



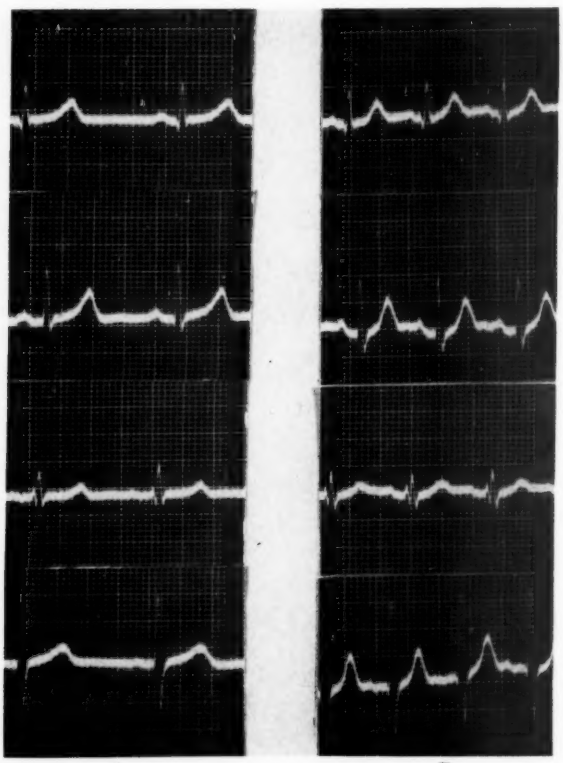
A. *B.*

Fig. 6.—Electrocardiogram (*A*) before and (*B*) after exercise. Woman (U 54971), aged 60. Angina pectoris with pain was produced on exercise. Note changes in T_1 and T_2.

The variability of the T-wave changes in the control group was striking. A variation in voltage of the T waves, as well as a change from an inverted T wave to an upright one, was commonly found. The only significant change, however, was the development of an abnormal T wave from one that had previously been normal.

In cases of angina pectoris, careful study of axis deviation, Q waves, and rate changes did not reveal anything significant as compared to the control series. Occasionally a patient showed slight prolongation of the P-R or QRS interval, extrasystoles, or minor P-wave changes after exercise. The significance of these changes was not ascertained.

The electrocardiographic changes after exercise in cases of angina pectoris are not dependent upon the production of pain, as is illustrated in the tables, although the percentage of positive results is much greater if pain is induced. When pain is produced by exercise, objective electrocardiographic evidence is obtained in two-thirds of the cases; when pain is not reproduced by exercise, only one-third of the patients have significant electrocardiographic abnormalities. The importance of the chest lead must be stressed, for eight of the thirty-seven significant changes occurred in Lead IV alone. This explains why we had a much greater number of positive results than previous workers who did not use chest leads. Of course, one should use a combination of limb and chest leads.



A. *B.*

Fig. 7.—Electrocardiogram (*A*) before and (*B*) after exercise. Control subject, woman, aged 25. Note S-T segment contour in Lead II as contrasted with the abnormal S-T contour in Fig. 3.

More positive curves might have been obtained if serial tracings had been taken at varying intervals after exercise; if some of the patients had been exercised more strenuously; if patients suffering from arthritis and intermittent claudication had been given a different type of exercise; or, if the characteristic contour of the S-T segment had been added to

the criteria. The criteria that have been established may have to be altered upon further investigation.

Changes caused by exercise offer objective evidence of angina pectoris (coronary insufficiency), but a normal response does *not* rule out the presence of coronary insufficiency.

CONCLUSIONS

1. Objective evidence of angina pectoris can be obtained from electrocardiographic changes in two-thirds of all cases if the pain is reproduced by exercise, and in only one-third if the pain is not reproduced by exercise. Significant electrocardiographic changes developed after exercise in 56 per cent of our patients with angina pectoris, irrespective of the absence or presence of pain.

2. In cases of angina pectoris, the significant electrocardiographic changes after exercise are: S-T segment depression or elevation of 1.0 mm. or more in Lead I, of 1.5 mm. or more in Lead II, of 1.5 mm. or more in Lead III, and 2.0 mm. or more in Lead IV; or the conversion of an upright to a diphasic or inverted T wave in Lead I, II, or IV; or the development of bundle branch block. If any one of these changes occurs, the electrocardiogram is considered abnormal.

3. The use of the chest lead increases the number of abnormal curves by approximately 20 per cent.

4. A normal response to exercise does not rule out angina pectoris.

We wish to acknowledge the technical assistance rendered by Miss Ola E. Nagle.

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THE VASOMOTOR CENTER ESSENTIAL IN MAINTAINING RENAL HYPERTENSION

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IT HAS already been noted that, in the rat[1] and rabbit,[2] destruction of the central nervous system reduces the arterial pressure of animals with renal hypertension to the same level as that of pithed controls. Since pithed animals are notably sensitive to pressor agents such as pitressin, epinephrine, tyramine, and renin,[3] it seemed highly improbable that a peripherally acting vasoconstrictor was present in rodents with renal hypertension. It was more reasonable to assume that the renal pressor hormone acted upon and through the vasomotor control mechanism.

As variation with species must be considered, these observations have now been extended to a carnivore, the dog, and the effect of section of the brain stem above the pons has also been studied. Neither the latter procedure nor section of the spinal cord at C_4 reduced the pressure of dogs with renal hypertension to levels approaching those of controls subjected to the same procedures. Complete destruction of the neuraxis in dogs does abolish the pressure difference between control and markedly hypertensive animals.

METHODS

Hypertension in dogs was produced by encasing both kidneys in gauze and collodion jackets; in some cases one renal artery was ligated a month or so later. Not all animals became hypertensive, but, within seven to fifteen weeks, most did, and in some this was so severe as to cause retinal separation, extreme irritability, and loss of weight.

Morphine-ether anesthesia was induced before performing the laminectomies, trephinings, and tracheal and carotid cannulations which were necessary for the final experiments. Artificial respiration was started before pithing and maintained thereafter; the blood pressure was recorded from the carotid artery by a mercury manometer. In some instances pithing was performed through a laminectomy, but in most cases through a small parietal trephine opening. Pithing was performed with three heavy wires twisted together, with a heavy solder bead at the tip, and spiralled so that, after insertion and rotation, the medulla and cord were effectively destroyed.

In order to sever the brain stem rostral to the pons, a trephine opening to the right of the vertex was extended with rongeurs down into the temporal bone, and a linear incision in the dura was made. When the other operative procedures were

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complete, and a control level of blood pressure recorded, an open clamp was introduced with one blade on the floor of the skull and the tip of the other near the vault. When this had been inserted as far as possible, the clamp was closed. Subsequent dissection, fixation, and midline section of the brain showed that the crushed tissue included parts of the parietal and temporal lobes, cerebral peduncles, and the brain stem at a level from the middle to the front of the corpora quadrigemina above, and the mammillary bodies, or the tissue within 1 cm. caudal to them, below.

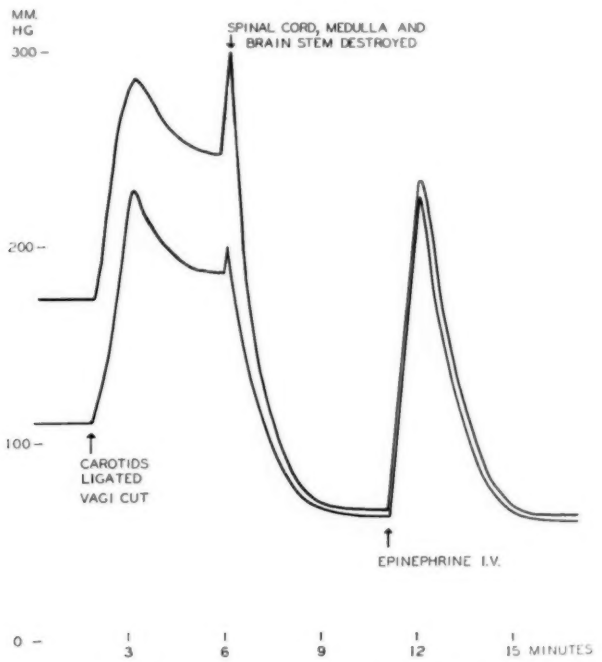

Fig. 1.—This is a composite of the arterial pressure changes in fourteen hypertensive dogs (upper curve) and twelve controls as the moderator nerves were eliminated, the animals pithed, and epinephrine (12 to 15 gamma per kilogram) given intravenously. Artificial respiration throughout.

RESULTS

In three hypertensive and three control dogs it was noted that only a slight fall in pressure occurred when the cervical cord was cut at C_3 or C_4 under ether anesthesia; the rise in pressure consequent on carotid ligation and vagus section was not strikingly diminished. These facts are of interest, for Root and McAllister[4] have shown that, in dogs which have regained a normal arterial pressure level after cord section, ether anesthesia leads to a profound fall in pressure, and Lim and his coworkers[5-7] have observed that crushing the cervical cord of dogs under cholalose anesthesia causes little fall in pressure and does not prevent a rise on stimulating the central stump of the severed vagus. Pithing the cord below C_4 led to a drop in pressure which was more marked in the hypertensive than in normal animals, but the average level of the

hypertensives after pithing in this way was 102 mm., and that of normals, 81 mm. Hg. This merely confirmed the observations of Glenn and his co-workers,[8, 9] who reported an immediate drop in the pressure of both hypertensive and normal dogs on destroying the cord below C_4, but with a higher level persisting in the hypertensives.

TABLE I

EFFECT OF LIGATING THE DOG'S COMMON CAROTID ARTERIES AND CUTTING THE VAGI TO ELIMINATE THE MODERATOR NERVES, AND OF COMPLETE PITHING

NO.	ARTERIAL PRESSURE (MM. HG)									
	CONTROLS					RENAL HYPERTENSIVES				
	A	B	C	D	E	A	B	C	D	E
1	115	205	202	70	250	190			88	
2	110	265	200	70	215	145			90	250
3	105	210	175	65	240	155	240	225	50	
4	85	220	140	80	210	225	340	275	80	270
5	115	235	170	60	220	165	300	280	70	270
6	90	270	200	60	210	145	250	190	50	190
7	130	245	215	60	230	147	240	230	65	230
8	125	270	210	50	260	200	320	255	60	200
9	118	225	210	55	195	200	295	260	50	195
10	125	200	175	80	225	212	340	250	80	260
11	115	185	170	60	230	175	245	220	50	230
12	100	220	150	50	210	175	275	260	60	240
13						160	305	295	67	210
14						145	285	245	63	260
Av.	110	229	185	63	226	174	286	248	66	234
% difference, hypertensives						+58	+29	+34	+4.5	+3.5

Column A, initial mean carotid pressure; B, peak reached on cutting the vagi; C, stabilized level after vagal section and prior to pithing; D, level established after pithing; E, peak of the response to epinephrine in the pithed dog. The hypertensive dogs had chronic perinephritis (I. H. Page's method).

It was noted, however, that, when the entire neuraxis was destroyed, the pressure of fourteen hypertensive dogs fell to 50 to 90 mm. (average, 66 mm.; and that of twelve control animals to 50 to 80 mm. (average, 63 mm.). The rise on giving epinephrine reached 234 mm., on the average, in the hypertensive pithed animals, and 226 in the pithed controls. It thus became evident that, although dogs pithed under ether are responsive to a peripheral vasoconstrictor such as epinephrine, they show no evidence of a circulating vasoconstrictor substance, even when renal hypertension is marked at the time of pithing.

Cutting off the flow of impulses from the carotid sinus and great vessels by carotid ligation and vagal section caused a marked rise in pressure in normal dogs, and also in the hypertensive dogs. The peak pressure reached in the hypertensives was 112 mm. (65 per cent) above the control level, and the pressure became stabilized 74 mm. (42 per cent) above the control value. In controls the peak was 119 mm. (104 per

cent) above the control; the stabilized level was up 75 mm. (+68 per cent) from the control figure. It was from these stable levels that the pressures fell to 66 and 63 mm. on pithing (Fig. 1 and Table I).

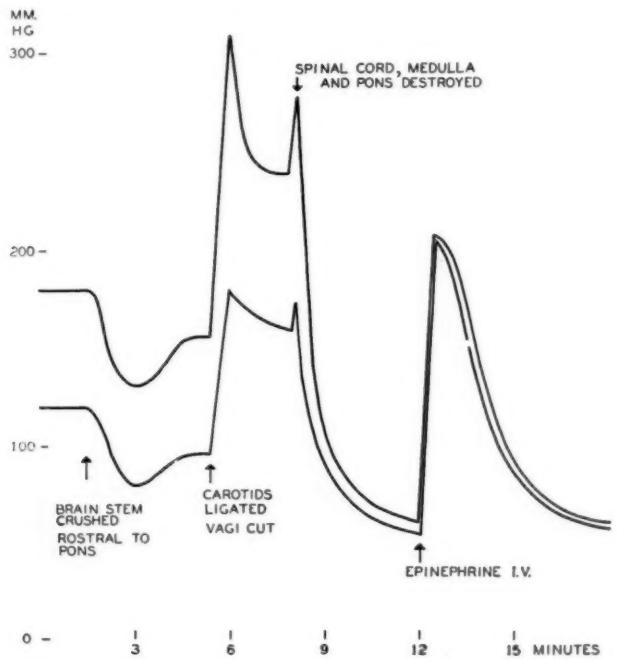

Fig. 2.—This is a composite of the arterial pressure changes in five hypertensive, but only two control, dogs (lower curve), which were subjected to destruction of the brain stem rostral to the pons, then to elimination of the moderator nerves, pithing, and intravenous injection of epinephrine. The brain stem was crushed with a hemostat; the line of crushing passed through the anterior half of the corpora quadrigemina, and through, or just caudal to, the mammillary bodies.

TABLE II

EFFECT OF CRUSHING THE DOG'S BRAIN STEM AT THE LEVEL OF THE CORPORA QUADRIGEMINA, THEN LIGATING THE CAROTIDS AND CUTTING THE VAGI, AND, FINALLY, COMPLETE PITHING

DOGS	ARTERIAL PRESSURES (MM. HG)						
	A	B	C	D	E	F	G
Controls							
C 1	125	65	87	170	170	60	230
C 2	115	95	105	185	150	50	180
Hypertensives							
H 1	200	100	115	200	180	50	180
H 2	150	92	130	300	270	60	190
H 3	160	130	195	270	255	65	190
H 4	182	160	160	310	195	60	200
H 5	220	180	207	360	285	80	260

Column A, initial pressure level; B, lowest level after crushing the brain stem; C, stable level after crushing; D, peak reached after vagal section; E, stable level before pithing; F, level established after pithing; G, peak of the response to epinephrine.

Five hypertensive dogs, but only two controls, were used to study the effect of destroying the brain stem rostral to the pons. The extensive

trephining and the crushing of the brain stem led to considerable blood loss, so that it was not surprising that, in response to epinephrine, the blood pressure after complete pithing rose only to 205 mm. in controls, and to 207 in the dogs which had been hypertensive. Nor was it surprising that the rise on cutting the moderator nerves and tying the carotids reached only 178 mm., and leveled off at 160 mm. in the controls, instead of reaching 229, as it did in controls with brain stems intact. However, in the hypertensive dogs the rise on vagal section and carotid ligation reached 308 mm., on the average, when the brain stem had been cut, which was 22 mm. higher than it went in those with intact brain stems. Although the crushing of the brain stem caused a transient fall, with partial recovery, it is obvious that structures rostral to the pons are not needed for the maintenance of renal hypertension or for the pressor response on cutting off the inflow from the moderator nerves (Fig. 2 and Table II).

DISCUSSION

From these observations it is apparent that the dog, like the rat and rabbit,[1, 2] does not have any demonstrable peripherally acting vasoconstrictor substance at a time when it is markedly hypertensive as a result of renal manipulation. In the rabbit it was proved that the fall of blood pressure on pithing was not due in any significant degree to shock, with low venous pressure. The venous pressure fell very little on pithing; raising it far above the control level by intravenous infusion did not abolish the hypotension in pithed rabbits, whether controls or renal hypertensives, and on giving epinephrine a marked rise in arterial pressure preceded any change in venous pressure. Since pithed carnivora are known to be exquisitely responsive to injections of renin[3] and other pressor substances, it seems certain that, if such substances were present in renal hypertension, pithing would accentuate the pressure difference between these animals and controls. Instead, it abolished the pressure difference.

It is realized that neither sympathectomy[10-12] nor destruction of the cord below C_4[8, 9] abolishes the difference between normal and renal hypertensive dogs, although the latter procedure causes in both groups a striking transient fall, with return to the original levels in a few days. Just how the vasomotor center regains its control after such denervations is not known, but it has been repeatedly shown that hypothalmic stimulation[6] or stimulation of the central stump of the vagus[5-7, 13] causes a rise in pressure in dogs after severing all the structures in the neck save the carotid arteries and jugular veins. Humoral mechanisms, i.e., one involving the postpituitary[5-7, 13] and one involving the superior cervical sympathetic ganglia,[13] are available and may participate in vasomotor regulation after peripheral denervation. Such mechanisms presumably

become more effective in chronic experiments, so that acute, total destruction of the neuraxis must be used to test whether or not the vasomotor center participates in renal hypertension. Observations based on partial chronic denervation[8-12] led to the belief that the renal pressor hormone must act peripherally. This no longer seems tenable.

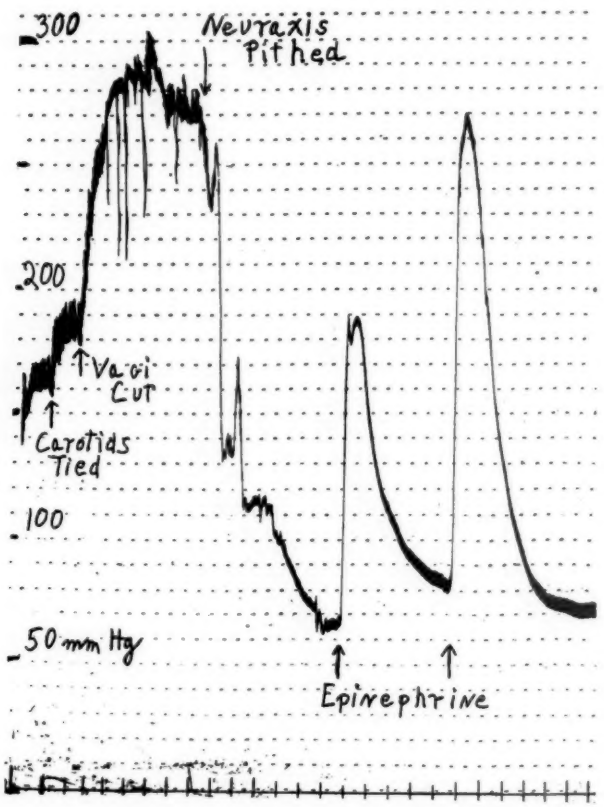

Fig. 3.—Arterial pressure curve, Dog 5, renal hypertensive group, Table I.

There is evidence that in man, also, renal hypertension is not due to peripheral action of a renal pressor substance. In the limbs, flow has been measured after maximal inhibition of vasomotor tone by warming the body, and by nerve block. This has revealed rates of flow equal to, or greater than, the flow in normal limbs under similar conditions.[14-17] One observer has found that the blood flow in the forearm under basal conditions is higher in hypertensives than in normals.[18] The most convincing proof was given by Pickering,[16] who studied flow in the vasodilated forearm of the same subjects during and after recovery from the hypertension of acute nephritis. Here, chronic trophic changes in vessels were eliminated, and there was no question that the hypertension was of purely renal origin. In every case the flow was higher when the

subject was hypertensive; the increase in volume per minute was proportional to the increase in pressure at the time of observation. The idea that there is a peripherally acting vasoconstrictor substance seems thus to have been completely disproved in the renal hypertension of man, as it has in the dog, rabbit, and rat.

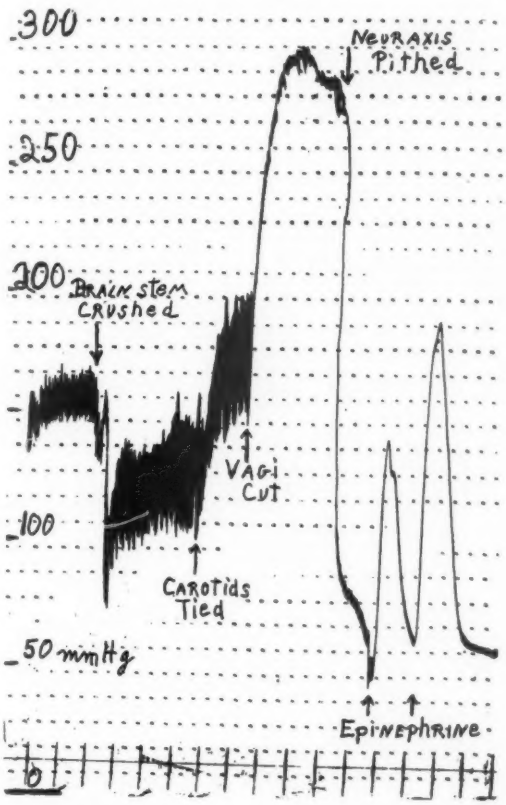

Fig. 4.—Arterial pressure curve, Dog H 2, Table II.

Peripherally acting vasoconstrictors, by raising arterial pressure, stimulate the nerve endings in the carotid sinus and great vessels, initiating reflexes which inhibit the outflow of vasoconstrictor stimuli from the vasomotor center. If one piths a rabbit or dog when it is hypertensive from the injection of such drugs as renin or epinephrine, no fall in pressure occurs because nervous vasoconstriction is already completely inhibited.[2] Under these circumstances, control over the circulation by the vasomotor center ceases once the pressure has been raised well above the normal level by a peripherally acting vasoconstrictor. In renal hypertension, both in man and animals, no loss or decrease in vasomotor control occurs; the pressure still rises in response to cold, pain, or loss of moderator nerve function; the flow in skin and muscles is still in-

creased in response to warmth or exercise. It therefore seems more reasonable to assume that the renal pressor hormone, in the concentrations reached in man and animals, in even the worst renal hypertension, does not act directly on the arterioles or usurp control from the vasomotor center, but acts to modify this control, i.e., to "set" the center for a high level. The effect of the kidney with an altered circulation upon the vasomotor center then can be likened to that of a myocardial infarct on the heat-regulating center. The latter causes fever, the former, hypertension, by changing the "set" of the control mechanism. However, this nervous mechanism in hypertension cannot be proved simply by lack of evidence of a peripheral vasoconstrictor; it must be ascertained whether the central nervous system, isolated from the general circulation and perfused by a renal hypertensive animal, will show such an altered vasomotor "set."

SUMMARY

Dogs with renal hypertension maintain arterial pressures above those of controls when, in both groups, the brain stem has been crushed rostral to the pons, or the spinal cord severed and destroyed below C_4.

Removal of moderator nerve impulses by carotid ligation and vagal section causes as marked and striking a rise in pressure in dogs with renal hypertension as it does in normal dogs. Renal hypertension is not due simply to partial inhibition of moderator nerve influences, for, if it were, complete loss of inhibition would result in the same pressure in controls and hypertensives.

Complete destruction of the central nervous system lowers the arterial pressure of dogs with renal hypertension to the same level as that of controls similarly treated; there is no evidence of a circulating, peripherally acting vasoconstrictor substance.

It is concluded that, in animals and man, the renal pressor hormone acts through the vasomotor nervous control mechanism; that it "sets" the center for a high level and does not act directly on the arteries.

I wish to express my indebtedness to Professor Hanzlik for the use of the facilities of the Department of Pharmacology.

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THE NORMAL DURATION OF THE Q-T INTERVAL

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A NUMBER of empirical formulas have been proposed to express the relation between the heart rate or cardiac cycle length and the Q-T interval of the electrocardiogram. The best known are those of Fridericia and Bazett. Fridericia[1] gave the duration of Q-T as $K\sqrt[3]{C}$, in which C is the R-R interval, or cycle length, and K is a constant, 8.22. This formula was found suitable by Schlomka and Raab,[2] who, however, state that K is 7.0 for infants, 7.95 for young people, and 8.25 in the aged. Bazett[3] proposed the formula $Q\text{-}T = 0.37\sqrt{C}$ for men, and $Q\text{-}T = 0.4\sqrt{C}$ for women. Fenn,[4] using the square root formula, employed a constant of 0.39 for both men and women. Several later authors[5] have agreed that these formulas are substantially accurate. A recent study indicates that Bazett's formula is more nearly in accordance with the facts when the heart rate is rapid and that Fridericia's applies when the rate is slow. Lipeschkin[6] says that the Q-T interval, as calculated, is too long by either formula when the heart rate is from 40 to 50 per minute. In rather sharp disagreement with others is Adams,[7] who, on the basis of the measurement of the Q-T intervals of fifty-one men and fifty-nine women, proposes the formulas, $Q\text{-}T = 0.1536\ R\text{-}R + 0.2462$ for men, and $Q\text{-}T = 0.1259\ R\text{-}R + 0.2789$ for women.

METHOD

In view of the fact that logarithmic formulas fit closely the course of many biologic processes, it seems remarkable that, so far as we can learn, no such formula has been proposed, except by Ashman and Hull.[8] In order further to test the validity of the formulas given by them, over 1,000 electrocardiograms on 432 men, 425 women, and 226 children were measured. The ages of the children ranged up to 14 years, and very few infants were included. The electrocardiograms were taken by means of a Hindle-Williams electrocardiograph over a period of twelve years.

Many of the tracings were from normal subjects, i.e., medical students and interns. The rest were from hospital patients who showed no electrocardiographic or other evidence of heart disease, with two exceptions. Since our experience had demonstrated that thyrotoxicosis, in the absence of heart disease, does not affect the Q-T interval, over sixty patients with this disease, nearly all women, were included in order to augment the number with short cardiac cycles.

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In order to make certain that this procedure was valid, the average value of the constant, K, in these cases, and the value of K for an equal number of normal subjects whose heart rates were in the same range were calculated. There was no significant difference between the averages.

A similar, but less rigorous, selection of normal subjects appears at the other end of the scale. Again, in order to augment the number, a considerable proportion of these records were taken on elderly patients, mostly men, who were suspected of having arteriosclerotic heart disease, but had no history of heart failure or cardiac infarction and had normal electrocardiograms and normal blood pressure. Our experience has indicated that in these cases the Q-T is nearly always within the normal range. All patients with hypertension were excluded. When sinus arrhythmia was present, the average cycle length was taken. Except among children, only a few measurements were included when the arrhythmia was conspicuous. Most of the shortest cycles (below 0.38 sec.) are from patients with supraventricular paroxysmal tachycardia.

The Q-T intervals of the adults were measured to the nearest 0.005 sec. by use of a hand lens. The average value of the measurements of several cycles was recorded. Care was taken to include the duration of the Q wave in the interval, no matter how inconspicuous that wave was. In nearly all cases, Q-T was measured in the lead with the highest T wave. Cycle lengths were measured to the nearest 0.01 sec. Among the adults, about a dozen wholly inadvertent duplicate readings were made on the same patient at different times. The children's Q-T intervals included forty to fifty duplicates. Fifty per cent of the data on children were taken from the measurements of Hafkesbring, Drawe, and Ashman,[9] and to the nearest 0.01 sec. Many of the same group, and a large additional number, were measured by the author, and all of the measurements were used.

RESULTS

Since it was found that, on the average, Q-T is slightly longer in the older subjects, we first present the data on all males between the ages of 15 and 32, inclusive. In Fig. 1 the data are averaged, and each point represents the cases included within a cycle length of 0.05 sec. The figures indicate the number of individual measurements which were averaged for each point. In deriving the average, points which fell, for example, on both cycle 0.725 sec. and cycle 0.775 sec., were included in the average for cycle 0.75 sec. Therefore, the sum of the numbers slightly exceeds the total number of cases. The curve is calculated from the formula, $Q\text{-}T = 0.375 \log [10(C + 0.07)]$. This is the formula of Ashman and Hull[8] for men and children. It gives a very satisfactory, although not perfect, approximation of the data. If K is taken as 0.373, the agreement is slightly better. The very similar formula, $Q\text{-}T = 0.370 \log [10(C + 0.09)]$ fits the data a little more closely.

Fig. 2 gives the data for all the females in the same age range. The formula of the curve is that given by Ashman and Hull for women, i.e., $Q\text{-}T = 0.385 \log [10(C + 0.07)]$. Here the agreement is almost perfect.

Fig. 3 combines the data for males and females between the ages of 15 and 32 years. In the construction of this curve, the individual female Q-T measurements were reduced, at each cycle length, by the vertical distance between the curves for men and for women, as given by Ashman and Hull. Fig. 3 is drawn from the formula, Q-T = 0.375 log [10(C + 0.07)]; this is the same as the formula previously given for men. For comparison, curve *B* is Bazett's formula, using the constant 0.39. Curve *C* is Fridericia's, with a constant of 8.0.

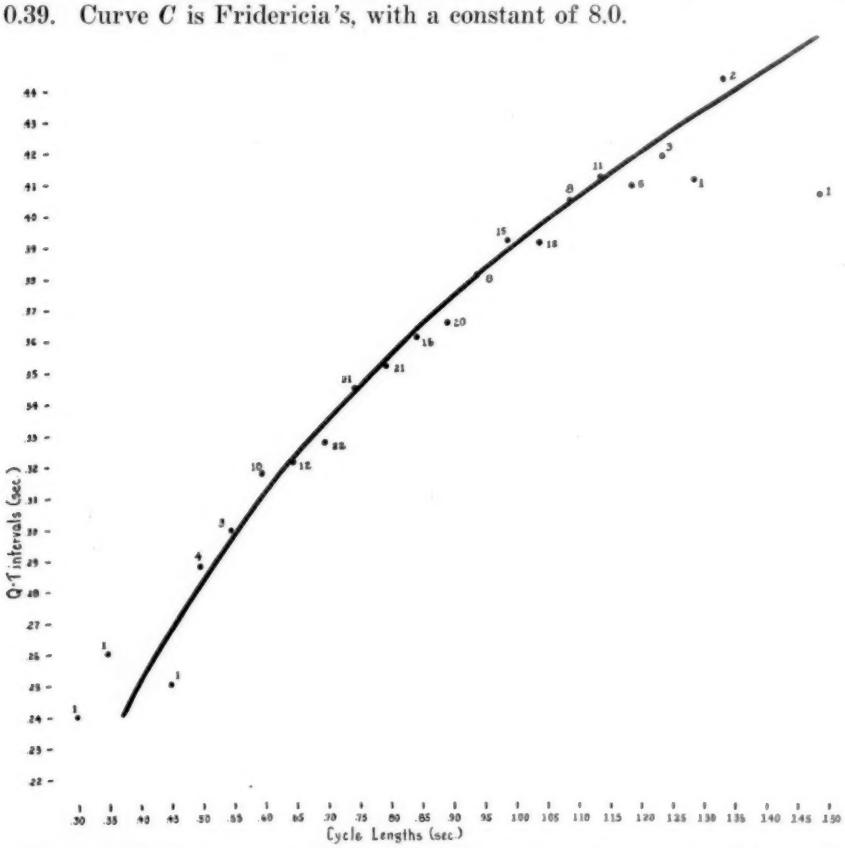

Fig. 1.—Young adult males. Each point is the average duration of Q-T in an interval of cycle length of 0.05 sec. The numbers indicate the number of cases included in each average. The curve is drawn to the formula, Q-T = 0.375 log [10(C + 0.07)].

When the measurements on all subjects 45 years of age, and older, are similarly treated, the curve, using a constant of 0.380, fits the average data closely.

Fig. 4 shows the scatter diagram for all the adult subjects. The curve which is drawn in uses a constant of 0.375. The agreement is excellent from cycle 0.40 sec. to cycle 1.00 or 1.10 sec. Beyond, the points range somewhat above the curve. A logarithmic curve will apparently not fit these data accurately and should not be expected to do so, for the averages at the longer cycle lengths include very

much higher percentages of middle-aged and elderly persons than those at shorter cycle lengths. Because of the influence of the disproportionate number of these older persons, the averages do not follow the curve but drift above it at slow heart rates.

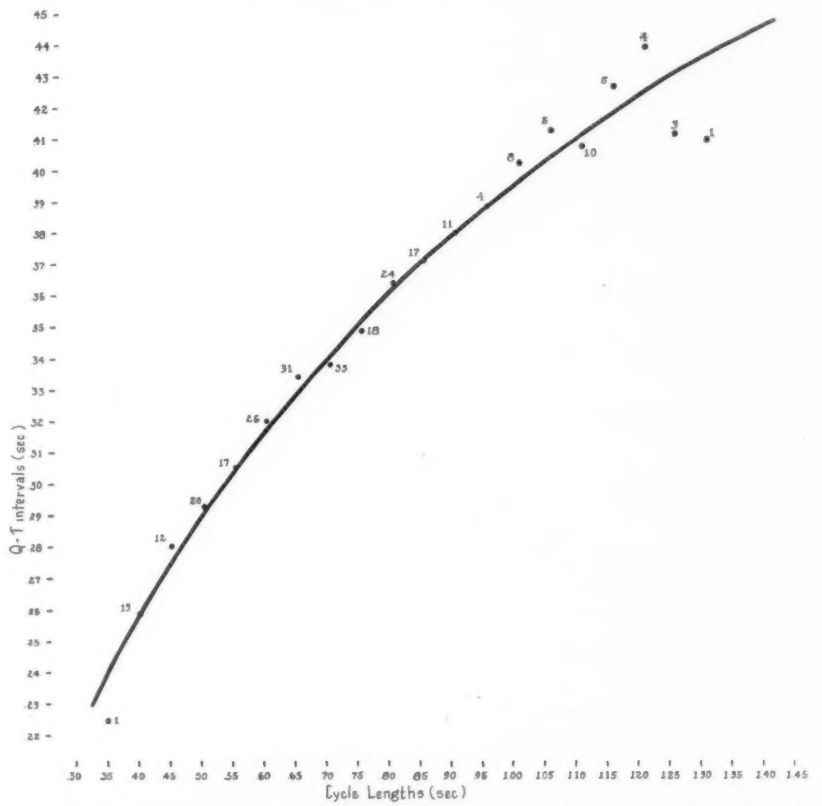

Fig. 2.—Young adult females. The formula for the curve is Q-T-= 0.385 log [10(C + 0.07)]. Otherwise as Fig. 1.

A curve drawn according to Ashman and Hull's formula for women, i.e., Q-T = 0.385 log [10(C + 0.07)], agrees very well with the data for all women, except at long cycles, where the influence of a disproportionate percentage of older persons again affects the average.

The data for children are less complete than for adults, but the curve fits the data fairly accurately. There are at least three factors which render the children's data less reliable than the adults'. One is the lack of a sufficient number of measurements at the extremes of heart rate. The second is that the frequency of sinus arrhythmia leads to error when the average cycle length is calculated, for the average on a short record may not be the true rate over a longer period of time. More important is the fact that the child is often more nervous than the adult, so that the heart may accelerate just before the record is obtained. With such

an acceleration, Q-T does not adjust itself immediately to the new rate; this fact has been recently re-emphasized by Blair, Wedd, and Young.[10] For boys of all ages, and for girls to the age of 12 or 13, the average value of K is 0.375. If the disturbing influences which have been noted were eliminated, the value would probably be the same as that for young adults. Mannheimer,[11] using Ashman and Hull's formula, has found that it fits his children's data very closely.

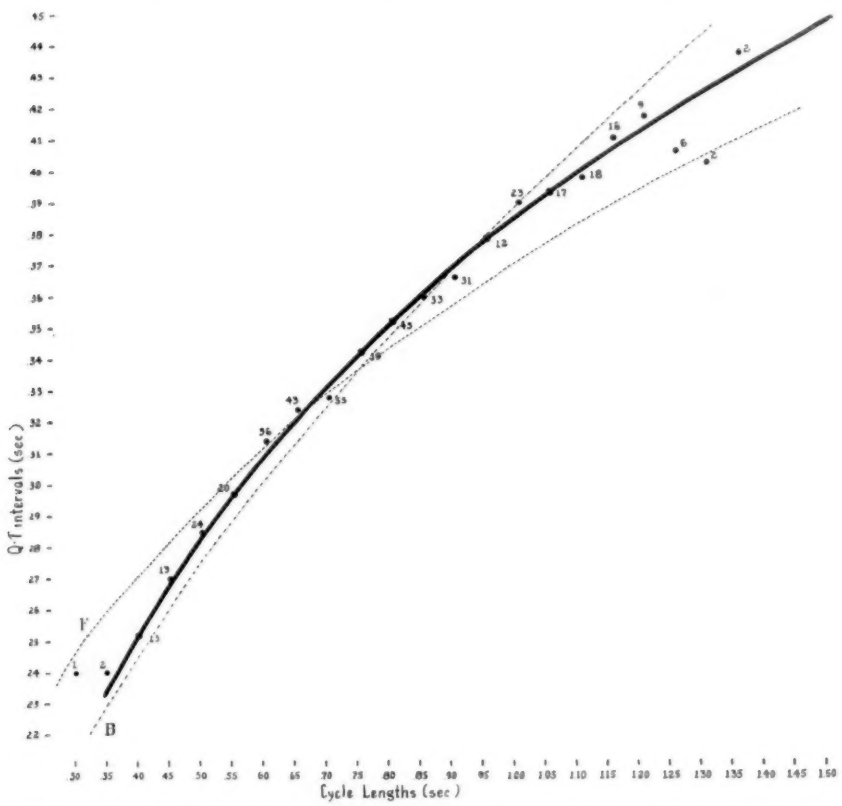

Fig. 3.—All normal subjects, aged 15 to 32 years; the points for women were lowered by the vertical distance between the curve for men, using K = 0.375, and, for women, using K = 0.385. *F* is Fridericia's curve, using a constant of 8, and *B* is Bazett's curve, using a constant of 0.39.

Fig. 5 represents the results of measurements of nearly 700 intervals from patients with heart disease. The arteriosclerotic-hypertensive etiology was predominant. The formula for the curve is Q-T = 0.405 log [10(C + 0.07)]. The Q-T intervals of the women were reduced by the distance between the curve for women with heart disease (K = 0.410) and that of men with heart disease (K = 0.405). This curve is included merely to demonstrate that here, also, a logarithmic curve fits the data closely. It may be noted that, when prolongation occurs, it is nearly, and perhaps precisely, in proportion to the Q-T

length characteristic of each cycle length. In other words, the lengthening is not by an absolute amount, such as, for example, 0.04 sec., at all heart rates.

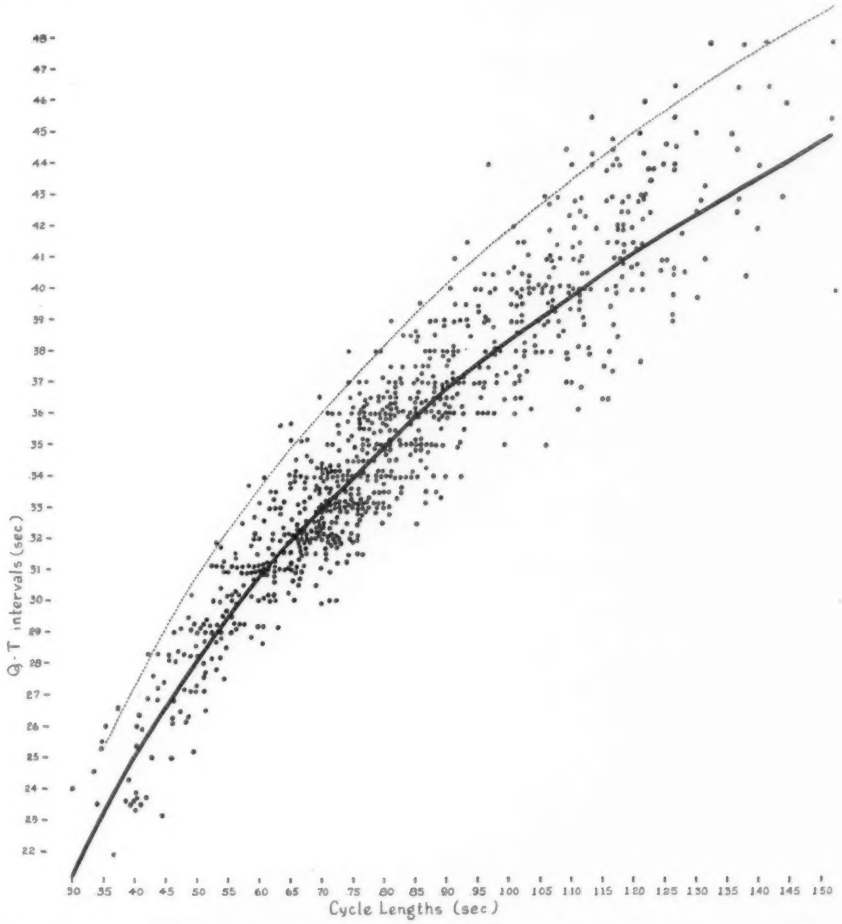

Fig. 4.—Scatter diagram of all adult subjects. Solid curve as in Figs. 1 and 3. Dotted curve is drawn from the same formula, using K = 0.41.

The upper limit of the normal Q-T interval was given by Ashman and Hull as a curve defined by a constant of 0.41 for men and 0.42 for women. In Fig. 4, the light, dotted line corresponds to the formula $Q\text{-}T = 0.41 \log [10(C + 0.07)]$, i.e., the upper limit for men. Since the points for women have been corrected to the male level, this formula will also apply to the women in this figure. It will be noted that only thirteen, or 1.5 per cent, of the points lie above this line by more than 0.005 sec.; this figure is within the error of measurement. Most of these longer intervals were from subjects over 33 years of age. This observation confirms the validity of the curve for the upper limits of the normal

as they were given. In this connection, it should be noted that this curve applies only to records in which the duration of the QRS complex is within normal limits.

The constant, K, can readily be ascertained for each individual interval by dividing the Q-T interval by log [10(C + 0.07)]. This has been done for all of the subjects. The frequency distribution of K for men and for women is shown in Fig. 6.

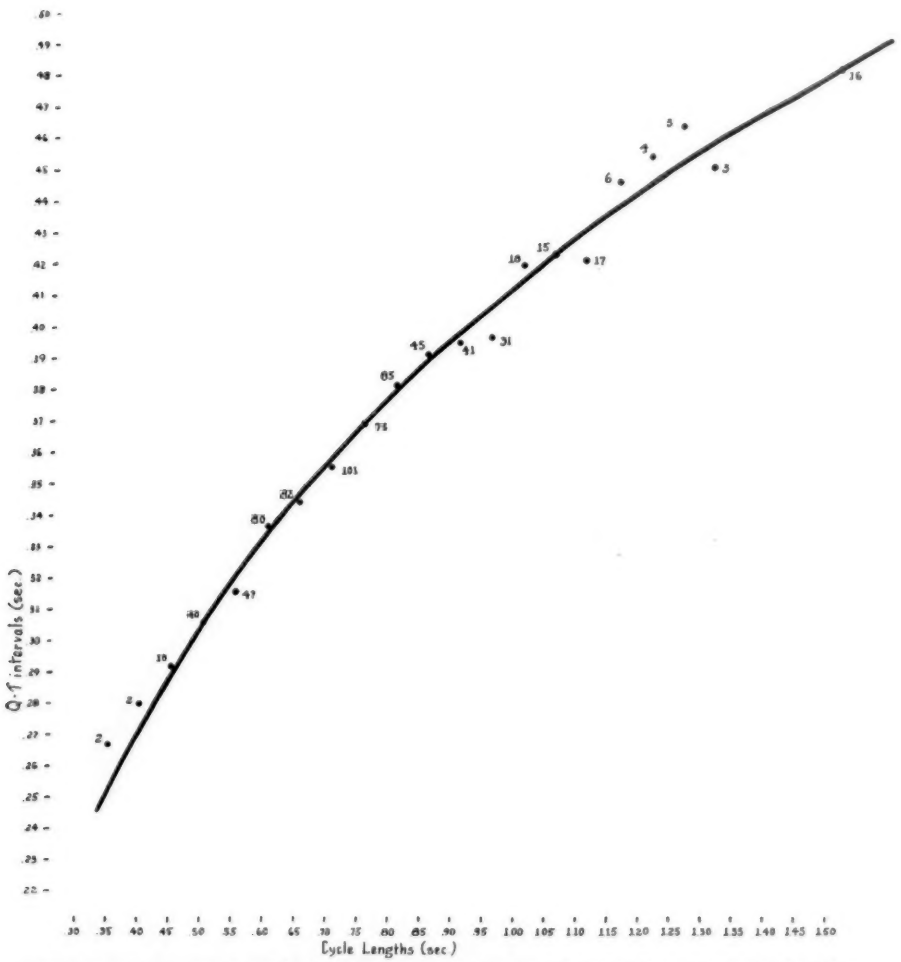

Fig. 5.—Averages of subjects with heart disease, predominantly of arteriosclerotic-hypertensive etiology (excluding thyrotoxicosis). Women's Q-T intervals adjusted. The formula for the curve is Q-T = 0.405 log [10(C + 0.07)].

In Table I the average values of K for 428 men and 412 women whose ages were known are given. Four cases of paroxysmal tachycardia among the men, with constants of 0.423, 0.418, 0.414, and 0.404, respectively, and four among the women, with constants of 0.425, 0.423,

0.393, and 0.391, respectively, are omitted from the averages for reasons given below. The average value of K for all the men was 0.377, and, for the women, 0.387. When these groups were subdivided according to age, the shortest average constants were found in the youngest groups. The difference between men and women is obviously statistically

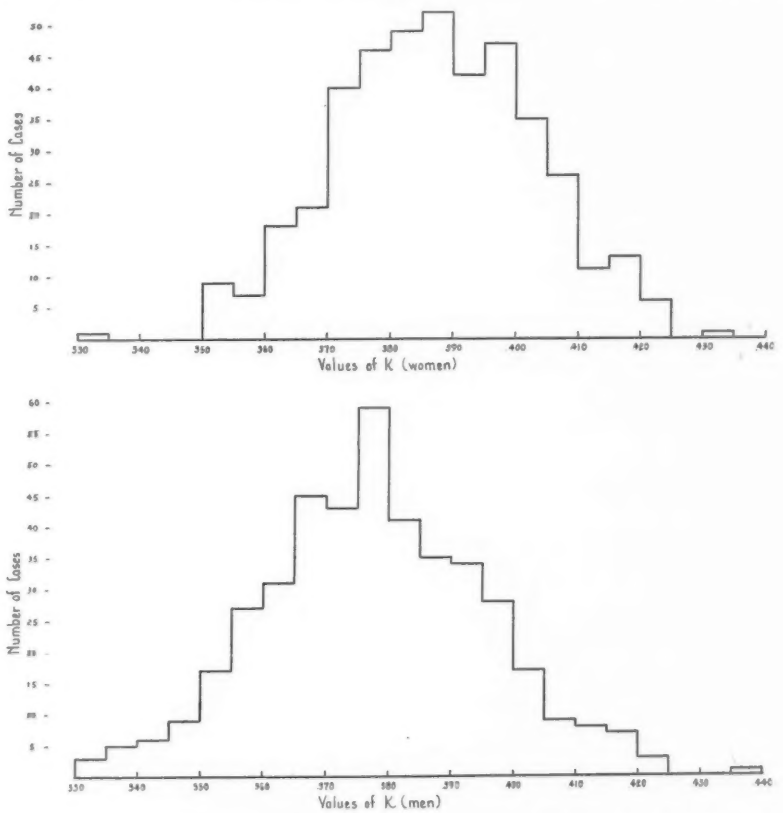

Fig. 6.—Frequency distribution polygons of the values of K for all the men (below) and all the women (above).

TABLE I

AGE (YEARS)	MEN		WOMEN	
	NO.	AV. K	NO.	AV. K
All	428	0.377	412	0.387
15-32	193	0.373	244	0.385
33-44	112	0.380	117	0.388
45 and over	123	0.380	51	0.390

significant and is reported by most of the students of this subject. The significance of the difference between the younger and the two older male groups has also been calculated. The probable error of the latter difference is ±0.0011, or less than one-sixth of the difference between the means.

The average value of K for 116 boys was 0.375, and, for 110 girls, 0.377. The age ranges for boys and for girls were from a few days to 15 years, and from a few days to 14 years, respectively. The difference between the average constants of boys and girls is too slight to be significant, but it is interesting to note that the average constant for the thirty-two girls between the ages of 12 and 14 years, inclusive, was 0.380. Their exclusion would reduce the average for girls practically to the average for boys. The prolongation of the Q-T interval from that of the child to that of the woman seemingly begins not later than at the age of 12 or 13. Although the mean value of K of the younger children tended to be shorter than that of older ones, no significant difference was found. Our figures suggest that, in early infancy, the Q-T may be slightly shorter, but a significant difference could not be established without a much larger number of measurements of normal infants. This is also suggested by Mannheimer's figures for children, mainly infants, with congenital heart disease.[11]

On the other hand, some of our intervals at higher heart rates may have been measured during a period of transitory acceleration caused by nervousness of the subject. This factor would tend to render these intervals slightly too long. The true curve, as ultimately constructed, may, therefore, be slightly, but perceptibly, steeper than the present one, and a slight adjustment of the constants may be required.

The difference according to age is much less than that reported by Schlomka and Raab,[2] who used Fridericia's formula. The large difference they observed between young children and adolescents, corresponding to constants of 7.0 and 7.95, respectively, almost certainly was due to their use of the cube root formula. This formula makes the calculated values for the more rapid hearts much too high. Consequently, in young children, whose average heart rates are high, a low constant must be used to force the curve to fit the average of the data.

Shipley and Hallaran[5] published scatter diagrams of 100 normal men and 100 normal women. The average K for both groups was calculated by us. That for the men was found to be 0.380, and, for the women, 0.393. The logarithmic curve given herein, using these constants, will be found to conform closely to their data. It is worth noting that the difference in K between men and women in Shipley and Hallaran's cases was 0.013; the difference between the constants for our younger subjects was 0.012. If the upper limit of the normal Q-T be placed at K = 0.410 for men, and 0.420 for women, one of Shipley and Hallaran's men reaches this limit and none exceeds it. On the other hand, four of their women exceed the upper limit, with constants of 0.443, 0.428, 0.424, and 0.421, respectively. Since, however, Shipley and Hallaran's measurements of Q-T were consistently slightly longer than those herein reported by about 0.01 sec., the upper limit for women should be raised,

to accord with their technique of measurement, to about 0.430. This would leave only one abnormally long Q-T interval in their group of 200 subjects.

White and Mudd[17] published a scatter diagram relating the Q-T interval of forty men, women, and children to the heart rate. If the rates are expressed in terms of cycle lengths, it will be found that their data also conform closely, except at the extremes of heart rate, to the logarithmic formula proposed herein if one uses a constant, K, of about 0.363 instead of 0.375. It will be observed that, although Shipley and Hallaran's Q-T measurements slightly exceed those herein reported, those of White and Mudd are considerably shorter.

DISCUSSION

The use of one formula for all human hearts may be criticized because the human curve is composite, representing many different persons, and may therefore not at all represent the curve as it might be derived from one heart. In fact, there is evidence[13, 17] that, if such a curve is constructed from one person's heart and the rate is varied by exercise or other procedures, the same slope is not always followed. But this work is open to the interpretation that, after a new rate has been attained, the rate must be kept at the new level for some time before equilibrium is established. Thus, the Q-T intervals during paroxysmal tachycardia were distinctly longer, on the average, than the calculated values, whereas, in thyrotoxicosis, even with almost equally rapid rates, the Q-T average was very close to that calculated. In the case of one male, a young physician with no evidence of heart disease, the Q-T interval during the paroxysm was nearly 0.03 sec. above the calculated value. After the paroxysm, at a cycle length of 0.65 sec., the Q-T was 0.28 sec., or 0.04 sec. shorter than the calculated value. In fact, it was shorter by 0.02 sec. than the Q-T of any other subject at this cycle length. On another occasion, the same subject had an electrocardiogram taken long after his last paroxysmal attack. The cycle was 0.655, and the Q-T, 0.32 sec., or just at the average length for men. We interpret this to mean that, after the paroxysm, a considerable period of time (more than enough to record all three leads) was required for the Q-T to lengthen to normal; whereas, during the paroxysm, insufficient time may have elapsed when the record was taken for the Q-T to have shortened to the characteristic length. On the other hand, it is possible to find electrocardiograms which show a rather prompt adjustment.

In any event, when electrocardiograms are taken under different conditions, as before and after meals, just after ordinary activity, while reclining, etc., the Q-T interval will vary with the heart rate at least approximately as the formula shows.[17] Since the phenomenon with which we are dealing is a fundamental one and since all human hearts are composed of practically the same protoplasm, we may anticipate

that a curve of Q-T intervals derived from a large number of persons with different heart rates will be of the same type (logarithmic) as a curve derived from a single subject, providing, of course, that, at each heart rate, equilibrium has been established.

It has been demonstrated that one of the factors which determine the duration of the Q-T interval is the blood calcium level.[14, 15, 17] As the ionized calcium level rises, the Q-T interval shortens, and vice versa. Intravenous injection of metaphosphate, which prevents the ionization of calcium salts, will markedly lengthen the Q-T interval in the dog. In the *Nitella* cell, according to the theory proposed by Osterhout and Hill,[12, 16] the action current is related to the movement of potassium ions. Perhaps the ionized blood calcium modified the Q-T interval by virtue of its well-known "antagonism" to potassium.

It is by no means established that the only factor responsible for prolongation of the Q-T interval in man is a decrease in calcium ions, even though it is probably true that the more conspicuous prolongations are associated with a low blood calcium. Heart disease, by disturbing the ionic balance in the cell, may possibly also prolong the Q-T interval. The Q-T interval is moderately prolonged in many cases of hypertension and aortic insufficiency, and is often more definitely increased in myocardial infarction after the acute stage. This is not due to widening of the QRS interval. Is the blood calcium reduced in these cases? In acute rheumatic carditis and among children who are convalescent from diphtheria, moderate prolongation of the interval is very common. It remains to be seen how important this is clinically, but it is my belief that this sign is very helpful in cases of suspected rheumatic carditis or myocardial ischemia. It has been pointed out that the sign may be useful in the diagnosis of uremia. If the interval proves to be of clinical value, it certainly becomes important to know accurately the normal relation between it and the cycle length and to know the normal range of variation.

Statistical methods have been applied in the study of our data only as indicated above. They are not needed when the quantity of data is adequate. The paper on this subject which makes most use of the statistical method[7] is easily in the poorest agreement with the observations of all other authors. Without at all decrying the application of statistical methods, which have great usefulness, the paper mentioned provides an example of the misleading sense of security which may be engendered by the use of the method with data which are insufficient. If the number of careful measurements were to be increased to, say, 10,000 and were evenly distributed throughout the range from cycle 0.30 to cycle 1.50, the curve would outline itself in the more densely packed areas at the median Q-T for each cycle length, and its definition, logarithmic or otherwise, would be a mere formality.

SUMMARY

The curve which expresses the relation between heart cycle length and the duration of the Q-T interval is logarithmic.

It may be represented by the general formula Q-T = K log [10(C + k)], in which C is the cycle length (R-R) in seconds. K and k are constants. The formula for women between the ages of 15 and 32 years, inclusive, is obtained by using K= 0.385 and k = 0.07.

The formula for younger men, and for children after early infancy, is derived by using K = 0.375 and k = 0.07. In these cases a slight change in both constants may possibly yield somewhat better agreement, but it is convenient and introduces a hardly appreciable error to use k as for women.

To patients 45 years of age, or older, the same formula applies, but with a K of 0.380 for men and 0.390 for women.

The upper limits of the normal Q-T interval may be expressed by the formulas previously published,[8] with allowance for personal variations in the technique of making the Q-T measurements.

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RAYNAUD'S DISEASE

A Review of Its Mechanism, With Evidence That It Is Primarily a Vascular Disease

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SINCE Raynaud described the disease which bears his name there has been a difference of opinion concerning whether the disease is primarily one of the sympathetic nervous system or of the vascular system. With the help of information which we have obtained from studies on nonvasospastic patients after sympathectomy, we have attempted to elucidate some of the problems concerning the relationship of the sympathetic system to the cutaneous vessels. We are reporting three cases of Raynaud's disease, with special studies.

CASE REPORTS

Case 1.—F. C., a white man, 55 years old, entered the hospital Aug. 4, 1938, with the complaint of cold, painful hands and feet. He stated that for the preceding four or five years his hands and feet would become numb and white and would ache and sting when exposed to cold. He had found it necessary to take the special precaution of wearing several pairs of woolen garments.

Examination.—The patient was of average weight and height, and appeared normal. He did not seem nervous or emotionally unstable. The general physical examination was essentially negative except for the fact that he was edentulous and had been operated on for relief of a hydrocele on the right side. Temperature was 98.6° F.; pulse rate, 72; respiration, 18. The blood pressure was 125/80 in both arms.

His fingers and toes felt cool, but did not appear particularly abnormal at room temperature. After immersing his hands in ice water for thirty seconds, there were scattered areas of blanching on the palms, and the skin over the distal two phalanges of the fingers became pallid. This color change was accompanied by aching and stinging pain. Two to three minutes after the hands were removed from the water the blanching disappeared.

On a previous admission to the hospital, April 2, 1938, an ice water test was done. Blanching of the fingers occurred when they were in the ice water, but the color returned to normal at room temperature. He was taken outdoors, where the atmospheric temperature was 20° F. His fingers became extremely pale; there was the usual aching pain; and, in fifteen minutes, the color changed through a red to a cyanotic hue.

The radial, popliteal, posterior tibial, and dorsalis pedis pulses were present, equal, and of good quality on the two sides. There was no evidence of trophic change on the fingers and toes.

Laboratory Study.—The urine and blood were normal. The blood Wassermann reaction was negative.

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Diagnosis.—Raynaud's disease (confirmed by Dr. Edgar V. Allen).

Treatment.—X-ray irradiation of the sympathetic chains was advised, but, since there was some question concerning the efficacy of irradiation, it was finally decided to do a cervicodorsal ganglionectomy on one side, and irradiate the other side.

On Aug. 6, 1938, the left inferior cervical and first and second dorsal ganglia were removed. This was followed by a Horner's syndrome on the left, and the left hand became obviously warmer than the right. The aching, stinging pain incident to exposure to cold was abolished on the left.

Recovery was uneventful, and he subsequently received 1,200 roentgen units over the corresponding ganglia on the right side. No evidence of subjective or objective improvement was observed as a result of the irradiation. He was discharged Aug. 22, 1938.

FOLLOW-UP EXAMINATION AND SPECIAL STUDIES

The patient returned to the hospital March 25, 1940, approximately twenty months after his operation. His general condition was essentially the same as on the previous admission, except that he felt that his feet and right hand were growing worse, i.e., he had more pain on exposure to cold. His left hand had been entirely devoid of pain since the operation.

The difference in the temperature of the fingers on the two sides varied from time to time at room temperature. At times there was no difference, and at others, the fingers of the left hand were 4.5° C. warmer than those on the right. Only on one occasion (before the adrenaline test) were the third, fourth, and fifth fingers slightly colder on the left side.

A thermoregulatory sweating test revealed absence of sweating in the usual distribution after removal of the inferior cervical and first and second dorsal ganglia. This included the left side of the face, neck, upper extremity, and chest down to the level of D 3. There was no evidence that regeneration had occurred.

We studied the skin temperature in the heating cabinet, refrigerator, after intravenous injection of adrenaline, and after administration of pilocarpine. The results are incorporated in Tables I, II, and III.

TABLE I

THE EFFECT OF HEAT (INDUCTOTHERM PLUS ATROPINE) ON THE SKIN TEMPERATURE

TIME (P.M.)	3:10		3:12	3:16	4:20		DIFFERENCE IN FIRST AND LAST READINGS	
	RIGHT	LEFT			RIGHT	LEFT	RIGHT	LEFT
Skin temperature average for fingers (° C.)	4.3	7.2			9.0	9.0	4.7	1.8
Mouth temperature	37.0° C. 98.6° F.				38.0° C. 100.4° F.			
Pulse rate	88				144			
B.P.	140/80				120/70			
Remarks	Basal		Atropine, gr. 1/75 (H)	In cabinet				

Room temperature, 26.0° C.; cabinet temperature, 45.5° C.

METHOD

Skin temperatures were taken with the Tycos dermatherm.* Before beginning an experiment, the patient was exposd from twenty to thirty minutes at a constant

*Taylor Instrument Co., Rochester, N. Y.

TABLE II

EFFECT OF ADRENALINE ON THE SKIN TEMPERATURE, MARCH 27, 1940

TIME (A.M.)	9:20		9:30	9:40		9:50		10:00		10:10		10:20		10:40	
	RIGHT	LEFT		RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT
Skin temperature average for fingers (° C.)	6.3	5.9	Adrenaline in saline, $\frac{1}{250,000}$—60 drops per minute	1.6	3.1	1.6	3.0	3.2	4.5	3.0	4.6	3.1	3.6	5.7	4.4
Mouth temperature	36.88° C. 98.4° F.			37.0° C. 98.6° F.		36.88° C. 98.4° F.		37.04° C. 98.7° F.		37.08° C. 98.8° F.		37.0° C. 98.6° F.		37.04° C. 98.7° F.	
Pulse rate	76			84		84		88		80		80		80	
B.P.	110/70			130/76		144/74		152/76		154/78		154/78		156/80	
Remarks	Basal														

Room temperature, 25.5° C.

room temperature, after which basal readings on various skin zones were taken. The mouth temperature, pulse rate, and blood pressure were followed throughout each experiment, and all observations recorded. The junction thermocouple was checked for each set of readings, and appropriate corrections were made, although this was rarely necessary. The figures recorded in the tables are the dermatherm readings, and hence indicate only the relative changes in temperature.

TABLE III

EFFECT OF PILOCARPINE ON SWEATING AND SKIN TEMPERATURE, MARCH 28, 1940

TIME (A.M.)	11:45		11:50	12:32		DIFFERENCE IN FIRST AND LAST READINGS	
	RIGHT	LEFT		RIGHT	LEFT	RIGHT	LEFT
Skin temperature average for fingers (° C.)	2.5	6.5	Pilocarpine, gr. 1/5, hypodermically	0.5	6.6	−2.0	0.1
Mouth temperature	37.0° C. 98.6° F.			36.4° C. 97.5° F.			
Pulse rate	72			76			
B.P.	128/90			130/90			
Remarks	Basal						

Room temperature, 25.5° C.

Comment on Heating Experiment.—We used the Burdick heating cabinet, i.e., dry heat and inductotherm. We have found that the administration of atropine in conjunction with the inductotherm results in the most marked dilator response of cutaneous vessels.[1] The inductotherm is so arranged that it affects the entire body.

At the beginning of the experiment the only significant difference in the temperature on the two sides of the body was of the finger tips, which were 2.9° warmer on the left. At the end of the heating experiment the temperature of the fingers was the same on the two sides. The mouth temperature rose 1.8° F. There was a fair amount of sweating toward the end of the experiment, except in the sympathectomized zone. There was marked capillary flushing which was limited to the right side of the face, right ear, and right hand. The line of demarcation between the flushed and unflushed zones on the face was definite. The significance of this phenomenon has been discussed.[1]

In this, as well as in the succeeding three experiments, the temperature changes of the forehead, ears, nose, cheeks, neck, chest, arms, forearms, palms, abdomen, thighs, calves, ankles and toes were also recorded. Since they revealed nothing particularly significant they were not included in the tables.

Refrigerator Experiment.—The method of carrying out this test has been given.[2] The patient is taken into the refrigerator nude, except for a loin cloth. At the beginning of the experiment the temperature of the fingers on the left side was 2.9° higher than on the right. At the end of the experiment the fingers on the left were still 1° warmer than those on the right, but actually the temperature of those on the left decreased over a greater range than on the right. Fig. 1 shows the fall in temperature of the fingers on the two sides (the readings are the average for five fingers). It can be seen that, after fifty minutes in the refrigerator, the temperature of the sympathectomized fingers dropped almost as low as did that of the unsympathectomized fingers. Indeed, at the end of the experiment the temperature on the two sides was more nearly equal than had been the case when the same experiment was done on nonvasospastic patients.[2] At any rate, we feel the important fact under the circumstances of this experiment, in which the whole body is exposed to cold, is that the sympathectomized fingers become almost as cold

objectively as the normally innervated ones. If the sympathetics had been playing a greater than normal role in this case, one would expect the intact side to show more vasoconstriction than that which had been operated on.

The subject began to shiver on entering the refrigerator, and continued to shiver until the end of the experiment. After fifteen minutes in the refrigerator both hands became blanched, the right slightly more so. After another five minutes the palms of both hands developed islands of mild flushing, with areas of pallid skin between. At the end of the experiment there was a mild, pink flushing of the hands, except for the distal two phalanges of all fingers. The latter were quite pallid, and remained so for one-half hour after being exposed to room temperature. The difference in the appearance of the two hands was one only of degree. The sympathectomized hand appeared only slightly less cyanotic in the nonblanched zones.

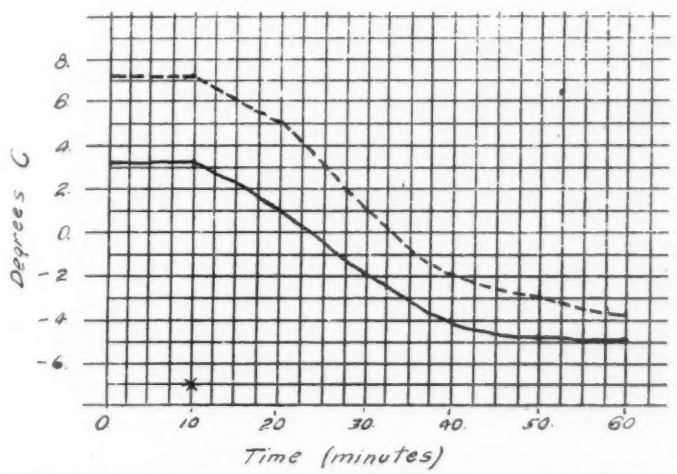

Fig. 1.—Graph illustrating the fall in the temperature of the fingers of F. C. in a refrigerator at 6° C. The temperature readings are those of the thermocouple, and are only relative. The basal readings were taken at room temperature (78° F.). Each curve represents the average for five fingers. The broken line represents the left (sympathectomized) hand. The unbroken line represents the right (intact) hand. *, Time at which refrigerator was entered.

The left (sympathectomized) hand subjectively felt warm, comfortable, and devoid of pain throughout the experiment, whereas the right hand felt cold and ached and stung as if it were penetrated by "a thousand needles." The feet felt like the right hand. The painful sensation in the right hand was marked after ten minutes in the refrigerator, at which time the relative temperature of the thumb was 2.0°. Ten minutes later the relative temperature of the left thumb also measured 2.0°, but no pain was felt on the left then or at any other time.

Comment on Adrenaline Experiment.—At the beginning of the experiment the temperature of the fingers on the two sides did not differ greatly. It is interesting that ten minutes after the adrenaline was injected (right median basilic vein), the temperature of the fingers on the right side fell 4.7°, which was greater than the fall on the left. This may have been an emotional response. At the end of one hour and ten minutes the temperature of the fingers was very little different on the two sides.

Comment on Pilocarpine Experiment.—At the beginning of the experiment the temperature of the fingers on the left was 4.0° warmer than that on the right. At the end of the experiment the temperature of the fingers on the right showed a fall of 2.0°, whereas that of the fingers on the left showed very little change. This is in keeping with our observations on nonvasospastic subjects. Our impression is that pilocarpine causes forced heat dissipation by its peripheral action (sweating and

vasodilatation). This is usually accompanied, as demonstrated in this case, by a fall in central temperature. The heat conserving mechanism then reacts, with a resulting vasoconstriction and usually shivering. Hence the normally innervated side becomes colder, whereas the sympathectomized side, which is disconnected from the central mechanism, fails to respond.

The patient experienced a desire to defecate and urinate, and began to sweat on the right side of the face, chest, and arm at 12:06. There was no evidence whatever of sweating in the sympathectomized zone. At 12:02 he began to feel cold except in the sympathectomized zone. The latter felt warm subjectively. This patient did not shiver. Patients usually shiver during this test, and state that they feel colder and more uncomfortable than when in the refrigerator.

SUMMARY OF CASE 1 (F. C.)

A 55-year-old white man with Raynaud's disease was studied twenty months after removal of the inferior cervical and first two dorsal ganglia on the left. Skin temperature was studied with the patient in a heat cabinet, in a refrigerator, and after the administration of adrenaline and pilocarpine. The observations indicated that the sympathectomy was complete for the left side of the face and upper extremity. This was true as regards sweat glands and cutaneous vessels; there was no evidence of sympathetic nerve regeneration. Pilocarpine anhidrosis was equivalent to thermoregulatory anhidrosis, indicating that the sympathectomy was postganglionic.[3] During the administration of adrenaline intravenously the temperature of the sympathectomized fingers did not fall materially. In a refrigerator the patient's hands developed the characteristic color changes of Raynaud's disease, and there was practically no difference in the appearance of the two hands. The left hand, however, was devoid of pain and felt warm subjectively, as has been the case ever since operation. The right hand ached and stung and felt quite cold.

CASE 2.—E. V., a white woman, 43 years old, entered the hospital May 22, 1940, complaining of limitation of motion in the joints and painful, cold, and white fingers and toes. About three years earlier she began to notice that at times the skin over the first phalanges of the fingers would grow pale and feel numb, and this would be followed by aching and stinging. This would persist for several minutes, after which the color would change to blue and then to red. The fingers would become normal again in about fifteen minutes. The attacks at first occurred only in winter, but later came on in the summer months, as well. For three years the left knee, right elbow, shoulder, wrists, and phalangeal joints had been growing somewhat stiff and painful.

Examination.—Physical and routine laboratory examination revealed nothing abnormal except the appearance of the hands and feet and early atrophic arthritic changes in the elbows, wrists, and phalangeal joints. The patient was not "high strung," nervous, or emotional.

The hands and feet were cold to the touch, and presented a thin, shiny, smooth skin which was devoid of hair. There were no ulcerative changes; roentgenologic examination revealed generalized atrophy of the wrists, elbows, and knees, without evidence of narrowing of the joint spaces.

When the patient's hands were placed in cold water for fifteen to thirty seconds, or when she was taken into a refrigerator, the terminal two phalanges of the fingers, particularly the index, middle, and little fingers, became dead white. The color change was accompanied by aching and stinging pain. After two to five minutes at room temperature the appearance of the fingers became normal again. In the hospital the blue phase of the color change was absent, although the patient stated

that it had been present at other times. Nevertheless, we felt the syndrome was sufficiently characteristic of Raynaud's disease to warrant the diagnosis, and the following experiments were carried out with the idea of ascertaining what influence the sympathetics have on the skin vessels, and whether this influence could be overcome by exposing the hand alone to a warm temperature.

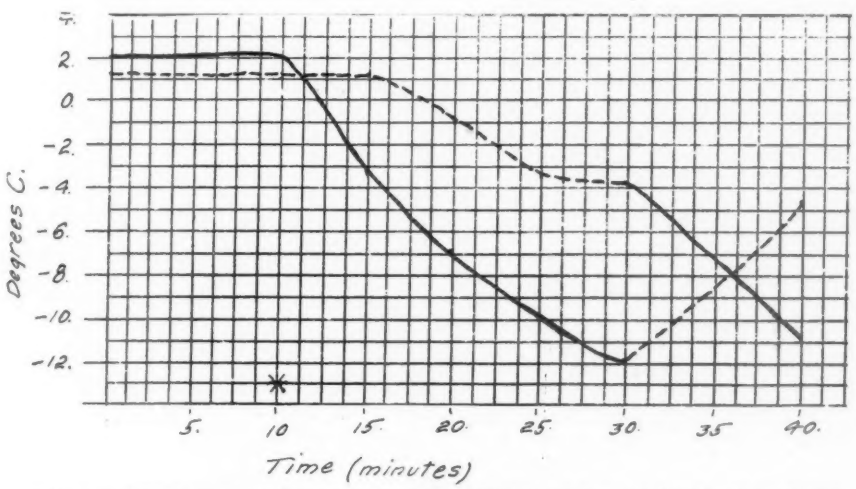

Fig. 2.—Patient E. V. was taken into a refrigerator, but her left hand was kept in a heated box. Curves represent the average skin temperature change of all fingers of each hand. Room temperature at which basal readings were taken, 25.0° C.; refrigerator temperature, 4.0° C.; temperature of heated box, 25.0° C.; solid line = right (exposed) hand; broken line = left (warmed) hand. *, Time at which refrigerator was entered. At the end of thirty minutes the right hand was placed in the warm box and the left was exposed.

Experiment 1.—We wished to expose the patient's body to severe cold, and, at the same time, keep one hand at room temperature. For this purpose a box was prepared and equipped with two electric lights and a thermometer. A hole was provided through which the patient inserted one hand and half of the forearm. Another hole could be opened just enough to permit an examiner to take the skin temperature. A glass window in the top provided a means of viewing the hand. The patient was exposed to room temperature (78° F.) for thirty minutes, and then basal readings recorded with the Tycos thermocouple. The absolute skin temperatures were not calculated. All readings represent only relative changes in skin temperature. The patient's left hand was fitted into the box with the palm up and resting on a square of felt. The patient, nude except for a loin cloth, then entered the refrigerator. The temperature of the refrigerator was 4° C., and that in the box was maintained at 25° C. The temperature of the finger tips of both hands was recorded at five-minute intervals. (Fig. 2). After ten minutes in the refrigerator the fingers of the right (exposed) hand blanched severely, felt quite cold, and stung with pain. The left hand, in the box, remained comfortable and of normal appearance for the twenty-minute period. At the end of this time the average temperature of the fingers of the exposed hand had fallen 14°, as compared to 5° for the left hand. The hands were then changed; the right hand was placed in the box, and, in ten minutes, the whole situation as regards temperature, appearance, and sensation was reversed.

Experiment 2.—The experiment outlined above was repeated, except that the temperature inside the box was maintained at 40° C. (Fig. 3). After forty minutes in the refrigerator the temperature of the fingers of the right (exposed) hand had fallen 17°, as compared to 1° for the left. The color changes and sensations were

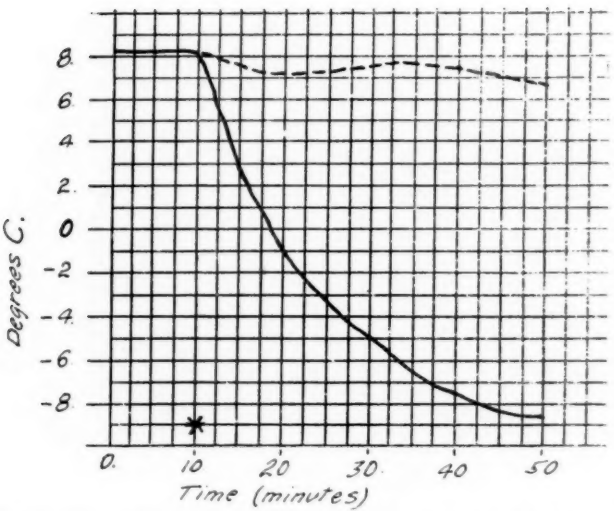

Fig. 3.—Patient E. V. was taken into a refrigerator, but his left hand was kept in a heated box. Curves represent the average skin temperature change of all fingers of each hand. Room temperature at which basal readings were taken, 27.0° C.; refrigerator temperature, 4.0° C.; temperature of heated box, 40.0° C.; solid line = right (exposed) hand; broken line = left (warmed) hand. *, Time at which refrigerator was entered.

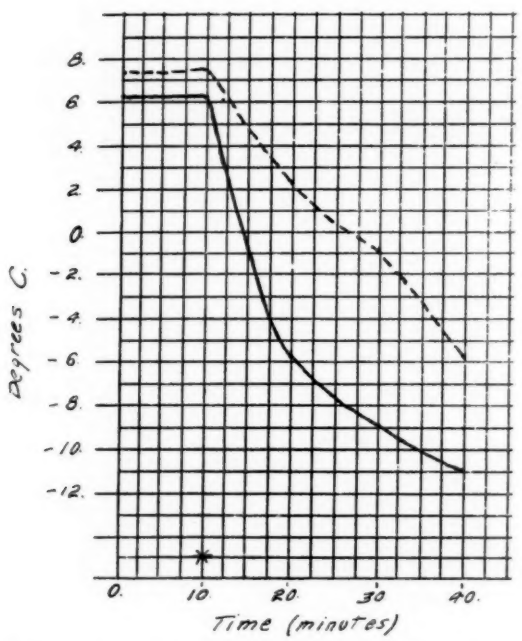

Fig. 4.—Curves showing the fall in temperature of the fingers of a nonvasospastic patient (N. B.) when the entire body was exposed in a refrigerator at 0°C. The right hand (broken line) was sympathectomized. The left hand (unbroken line) was normally innervated. Each curve represents the average of five fingers. At the end of the experiment the 5-degree difference on the two sides represents the vasoconstrictor activity of the sympathetics. The temperature readings are relative. *, Time at which refrigerator was entered.

the same as in Experiment 1. The left hand remained quite pink, and presented a few drops of sweat. After the forty-minute period in the refrigerator the mouth temperature of the patient dropped from 98.4° F. to 97.9° F.

Fig. 5.—Patient E. V. Thermoregulatory sweating test, using the starch-iodine indicator of Minor. There is complete anhidrosis above the skin level of D 3 on the right, and D 2 on the left.

Comment.—In Experiment 1 the fall in temperature of the fingers in the warm box reflects the influence of the sympathetics on the cutaneous vessels of the fingers when the latter are kept at room temperature and the body is severely chilled. We[2] have studied the skin temperature of patients in the refrigerator after unilateral cervicodorsal ganglionectomy. In this case both hands were exposed. These patients did not have vasospastic disease. At the end of such an experiment the temperature on the intact side fell to a lower level than that on the sympathectomized side, and we felt that the difference was an expression of the added influence of the sympathetics on the normal side. The difference in those cases agreed roughly with the difference at the end of twenty minutes in Experiment 1. For example, a non-vasospastic patient with a unilateral dorsal sympathectomy* was taken into the refrigerator with both hands exposed (Fig. 4). After thirty minutes the difference in temperature of the fingers on the two sides was 5° C.; the sympathectomized side was the warmer.

*Only the second dorsal ganglion was removed on the right. The thermoregulatory sweating test and the capillary vasodilatation test[1] proved that this was as complete a sympathectomy of the face and upper extremity (as far as central connections are concerned) as that which results from the removal of the inferior cervical and upper two dorsal ganglia.

Experiment 2 demonstrates that an environmental temperature of 40° C. about the hand can cancel any influence that central impulses through the sympathetics may tend to have, even when the body temperature is forced down 0.5° C. If the sympathetics played the major role in causing the abnormal vasospastic state, one would certainly expect it to be manifested to a greater extent than was demonstrated in these experiments.

On Aug. 19, 1940, a bilateral sympathectomy was performed by the dorsal extrapleural approach, as follows: *On the right*, segments of the second, third, and fourth ribs were removed. The sympathetic chain was severed below the third dorsal ganglion. All rami entering and leaving the second and third dorsal ganglia were severed. The cut end of this proximal segment of the chain was sutured to the nearest muscle. Rami to the inferior cervical and first dorsal ganglia were not molested. *On the left*, after removing segments of the first, second, and third ribs, the inferior cervical and upper two dorsal ganglia were removed. The patient therefore had, on the right, a preganglionic, and, on the left, a postganglionic sympathectomy. The sympathectomy was complete on both sides in so far as central connections were concerned, as indicated by a thermoregulatory sweating test* (Fig. 5). The right upper extremity was perfectly comfortable after the operation, but the left ached, burned, and was sore and tender for two or three months. The syndrome closely resembled peripheral neuritis, and has been of common occurrence in our experience, as well as in that of Brown and Adson,[5] after cervicodorsal ganglionectomy. We believe that it can be attributed to trauma to the cords of the brachial plexus incident to removal of the stellate ganglion.

The blanching of the fingers caused by exposure to cold or immersion in ice water was not abolished by sympathectomy on either side, and it was repeatedly observed and produced at will. The patient stated, however, that the blanching was now unaccompanied by the aching and stinging pain that she formerly experienced.

In a letter which was received seventeen months after the operation on this patient, she stated that her hands still undergo the same blanching and blue color changes when exposed to cold as they did before, but that they are now practically free from the former pain and discomfort.

Case 3.—M. S., a white woman, 26 years of age, was admitted to the hospital Jan. 26, 1941. For the preceding three years she had noticed that her hands became blue when they were exposed to cold. Later, her feet reacted in the same manner. Two weeks before admission the tip of the right thumb became gangrenous.

Examination.—Physical and routine laboratory examination was essentially negative except for the cold hands and feet. The tip of the right thumb was gangrenous, and the right hand was swollen and tender.

When the hands were immersed in cold water, they would become blanched, later blue, and finally pink. They ached severely when exposed to cold. This was obviously a case of Raynaud's disease.

Experiment 1.—The temperature of the fingers was recorded for a period of time under basal conditions as in the previous experiments. The left hand was then fitted into the warm box, as described under Case 2, and the patient taken into the refrigerator. The box was maintained at 40° C. for fifteen minutes, and then reduced to 30° for fifteen minutes. Two minutes after entering the refrigerator the right index finger began to sting and became dead white. In fifteen minutes the right hand blanched, became painful, and developed bluish islands over the

*The starch-iodine indicator of Minor[4] was used.

palm and dorsal surface. Throughout the experiment the left hand, which was in the warm box, remained pink and comfortable. There was never the slightest evidence of blanching. While the temperature of the box was being maintained at 40° C. the temperature of the left hand increased. When the box temperature was reduced to 30°, the temperature of the hand fell only 2° below what it had been under basal conditions. The temperature of the tips of the fingers was recorded every five minutes. Fig. 6 shows the average temperature of the fingers of each hand. The mouth temperature was reduced 0.5° F. in thirty minutes.

Comment.—This experiment again demonstrates the fact that a warm environment can completely annul any tendency the sympathetics might have to produce abnormal vasospasm, even when the body is chilled sufficiently to reduce the mouth temperature by 0.5° C.

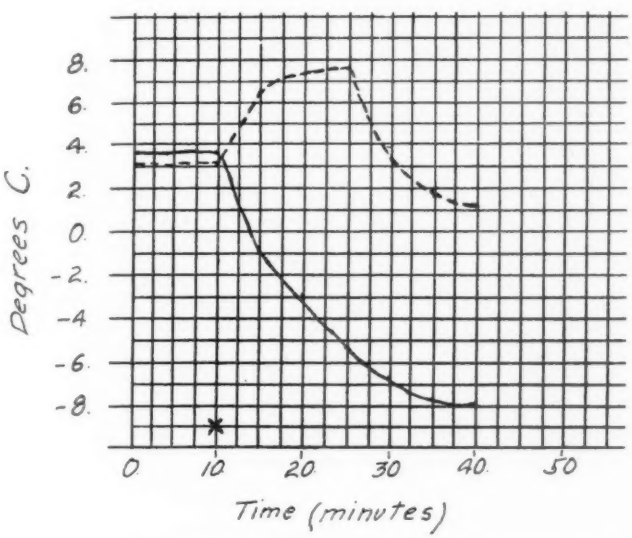

Fig. 6.—Graph illustrating the temperature changes in the fingers of M. S., Case 3. The temperatures were taken with a thermocouple, and represent only relative changes. The curves were computed from the average of the fingers of each hand. The broken line represents the values for the left hand, which was kept in a warm box. From ten to twenty-five minutes on the graph the temperature of the box was 40° C. Thereafter, it was maintained at 30° C. The unbroken line represents the values for the right hand, which was exposed to refrigerator temperature (5° C.). Basal readings were taken at room temperature (78° F.). *, Time at which refrigerator was entered.

Operation.—On Feb. 4, 1941, an upper dorsal sympathectomy was performed on both sides, as follows: *On the right,* all rami to the second and third dorsal ganglia were severed. The chain was severed below the third ganglion and the cut end sutured to the overlying muscles. The rami to the inferior cervical and first dorsal ganglia were not molested. *On the left,* only the second dorsal ganglion was removed.

Result in Respect to Completeness of Sympathectomy.—The thermoregulatory sweating test, which was performed several times, indicated that, in so far as central connections are concerned, the sympathectomy was as complete on both sides as is the case after cervicodorsal ganglionectomy (removal of the inferior cervical and upper two dorsal ganglia). On the right, the level of anhidrosis was one segment lower than on the left. This case constitutes further proof that it is necessary to remove only the second dorsal ganglion to obtain complete sympathectomy of the

face and upper extremity. This case, with photographs, will be presented in another report, along with evidence that supports this statement.

Result in Respect to the Vasomotor Abnormality.—The hands became several degrees warmer and considerably more comfortable. The swelling of the right hand subsided in four days, but it was subsequently necessary to amputate the right thumb.

Both before and after time for degeneration had been allowed, the color changes could be invoked by immersing the patient's hands in cold water, although she stated that the aching pain formerly associated with exposure to cold was greatly relieved. No differences could be discerned in the two hands as a result of the different types of sympathectomy. The result has remained satisfactory and beneficial to the patient up to the time of writing (nine months).

THE MECHANISM OF RAYNAUD'S DISEASE

Raynaud,[6-8] in 1862, presented a classical description of the disease that has since borne his name. Raynaud regarded the disease as primarily a disorder of the sympathetic nervous system, and thought that the lesion or locus operandi was situated in the lateral grey matter of the spinal cord.

This concept was accepted practically without exception until Lewis[9] presented evidence to show that the cause or locus operandi of the disease was local, in the vessel itself, and did not involve primarily the sympathetic nervous system. In spite of Lewis' work, writers have generally continued to agree with Raynaud's original concept, largely because of the beneficial results of sympathectomy in the treatment of the disease. Kerr,[10] however, in 1930, further supported Lewis' concept. Also, Morton and Scott,[11] in 1931, essentially concurred with Lewis, and stated, "Thus our opinion is that Raynaud's disease is not primarily due to an abnormality in sympathetic innervation, yet that the majority of the attacks except in the most severe cases are initiated or accentuated by vasoconstrictor stimuli under the ordinary living conditions of these patients." Boggon[12] and Gask and Ross[13] concur with Lewis, but advocate sympathectomy to increase the caliber of the denervated arteries.

We shall quote Lewis' concept in his own words, and then present briefly some of the criticisms of his contention. "Local applications of heat and cold show that the spasm is profoundly influenced by temperature, in response to which the vessels behave abnormally. These observations are opposed to the current view that the spasm is vasomotor in origin; the abnormal element in the reaction to cold is a direct reaction and due to a peculiar condition of the vessel wall locally; it is not the result of a reflex through the vasomotor nerves. The state of the vasomotor nerves naturally influences the tone of the vessels in these patients as it does in normal people, but the pathological element in the vascular spasm is not of nervous origin, as at present it is generally thought to be."

We feel that Lewis has pointed out a very significant phenomenon which discredits the idea that the vasospasm is the result of a sympa-

thetic reflex mechanism. He has shown that, when the finger of a patient with Raynaud's disease is immersed in cold water, the vasoconstrictor response is limited to the part immersed. Conversely, when a finger is immersed in warm water the release of spasm is local. Evidence has been obtained to show that when one leg of a spinal monkey is immersed in ice water, the temperature of the opposite foot will fall.[14] The magnitude of the fall is about 3° after approximately twenty minutes. Also, it has been shown in normal man that when an extremity is warmed, other skin areas will exhibit a rise in temperature.[15] This latter response has been attributed to the integrated action of the hypothalamus, which is, in turn, stimulated by changes in blood temperature. Hence it is known that reflex vasoconstriction can occur by means of reflexes through the spinal cord,* and also that vasodilatation can occur as a result of warming the hypothalamus. However, such reflexes are widespread and not limited to small areas of skin. It would require a great stretch of the imagination, in the light of what is known about the reaction of the sympathetic system, to attribute Lewis' results to anything but local vasoconstriction.

Lewis[16] studied six cases of Raynaud's disease after preganglionic sympathectomy. Discoloration of the fingers occurred spontaneously, or was induced, within a few days after operation in three cases. In two of the remaining three cases abnormal reactions to cold were produced with difficulty before operation but easily after operation. He expressed the belief that preganglionic sympathectomy did not restore the condition of the fingers to normal, for there was still a local abnormality similar to that which existed before operation.

White[17] states that the above observations of Lewis are well taken, but criticizes his interpretation of results because many of his subjects had incomplete sympathectomies, and because he studied advanced stages of the disease and did not explain an often concomitant abnormal activity of the sweat glands in Raynaud's disease.

Simpson, Brown, and Adson,[18] in their study of cases of mild Raynaud's disease, could not reproduce the color changes after local anesthesia of fingers or after sympathectomy, except in one case in which cervicodorsal sympathectomy was done. By wrapping the normally innervated hand in a blanket and exposing the body to cold, they produced the bluish color change in two cases. They agree that the local abnormality may be demonstrated after sympathectomy in cases of advanced Raynaud's disease.

Livingston[19] disagrees with Lewis' concept for much the same reasons as those given by White, but encounters the usual difficulty in ex-

*For convenience we like to designate the local responses to stimuli as *first order responses*, those through cord reflexes as *second order*, and those through the hypothalamus as *third order*.

plaining recurrences of the disease, particularly in the upper extremity. He attributes early recurrences to an incomplete operation, or to the fact that the disease may have been too far advanced, with secondary organic changes. He ascribes late recurrences not to regeneration, which he believes is improbable, if not impossible, after ganglionectomy, but also to incompleteness of sympathectomy. He goes so far as to say that, since removal of the inferior cervical and upper two dorsal ganglia does not always cure Raynaud's disease, this operation does not eliminate all vasomotor fibers to the upper extremity.

Simpson, Brown, and Adson[20] favor the view that Raynaud's disease is a disease of the sympathetics, and not a local vascular disease. They admit, however, that, when it is advanced, as Lewis pointed out, sympathectomy only modifies, and does not abolish, the vasoconstrictor response to cold. They also admit that, when it is severe, there is an abnormal response of the arterioles, but they attribute this to secondary changes that have occurred in the arteries and arterioles. In the discussion of their paper, Brown states, "In this connection it is interesting to recall that hypertension was once thought to be due to structural changes in the arteries. Sir Clifford Allbutt presented convincing evidence that the increase in blood pressure preceded the organic changes. The etiologic mechanism was determined by observation and study of the early, not of the late cases of hypertension."

We feel that this analogy to hypertension stands more in disfavor of the contention of Simpson, Brown, and Adson than in its favor, because the facts concerning essential hypertension are rapidly demonstrating that the peripheral arteriole can, and does, maintain a state of functional hypertonicity exclusive of its autonomic innervation.

Learmonth,[21] in referring to autonomy after sympathectomy, states that it is greater in some systems (alimentary) than in others (peripheral vascular), and that it is certain that interruption of vasoconstrictor and sudomotor pathways cannot be compensated for by intrinsic nerve mechanisms. Although the arteriole may be devoid of an intrinsic nerve mechanism, it is by no means devoid of automaticity after denervation.* The arteriole continues to respond myogenically (?) to chemical and thermal stimuli, and we[1, 2] have shown that when it is exposed directly to temperature changes the magnitude of the response is great.

Adson[22] contends that Raynaud's is a sympathetic disease because of the psychic influence on the changes in color and because the attacks may occur in a warm environment. He points out that high fever (elevation of 3 to 4° C.) abolishes the psychic influence and the cycle of color changes (attacks). He reported four interesting things after

*It is known that the capillaries of the skin manifest an "intrinsic" nerve mechanism through the axon reflex after sympathetic denervation. It is not known whether the arterioles may be governed by a similar mechanism.

sympathectomy: (1) There is no characteristic color change during exposure to cold; (2) attacks do not occur when the patient is excited or under emotional stress; (3) there are relief of local pain and disappearance of trophic changes; and (4) the retinal arteries are actually increased in diameter.

With regard to the psychic influence on the attacks, an important consideration arises. Although we believe that Raynaud's disease is caused primarily by an abnormality of the vascular system, we can see no valid reason why, in this disease, the skin arteriole is not more responsive or sensitive to sympathetic impulses than the normal vessel. If the arteriole in cases of Raynaud's disease is abnormally sensitive to cold, it is not unlikely that it would also be abnormally sensitive to otherwise normal sympathetic impulses. This in no way implies that Raynaud's disease is primarily a sympathetic disorder. The facts are somewhat difficult to establish, but the results of our experiments, particularly those illustrated in Fig. 1, would militate against the idea that, in Raynaud's disease, the vessel is abnormally sensitive to sympathetic impulses. Likewise, it is significant that the sympathectomized vessel in Raynaud's disease is not more sensitive to adrenaline than the sympathectomized, nonvasospastic vessel.[23] This has also been our experience.

We are not in agreement with Adson's first observation, as given above. In connection with his second observation, it is obvious that the direct nervous pathway through which emotional factors can evoke vasomotor responses is interrupted after sympathectomy. However, the indirect mechanism by which emotion can effect vasoconstriction, through the medium of adrenaline, forms the basis of White's[17] explanation of the poor results with the upper extremity. With respect to Adson's third observation, we feel that the relief of pain by sympathectomy is especially important and would of itself be an indication for the operation, but the fact that the pain is relieved does not prove that Raynaud's disease is primarily a sympathetic disorder.[2]

Telford[24] subscribes to the concept that Raynaud's is a sympathetic disease and attributes the poor results after sympathectomy of the upper extremities to incompleteness of the operation.

Thus a major difference of opinion exists concerning the etiology or mechanism of Raynaud's disease. Lewis, Kerr, Morton and Scott, Boggon, and Gask and Ross, as far as we know, stand alone in their belief that it is a primary vascular disease; others have adhered to Raynaud's original contention that it is primarily a disease of the sympathetic nervous system. The cases reported here, together with studies recently completed,[1, 2] strengthen Lewis' contention. The belief that Raynaud's is a sympathetic nervous system disease appears to be supported largely by the fact that the disease is benefited by sympathec-

tomy.* In the lower extremities the results are usually excellent and permanent after lumbar ganglionectomy, but in at least half the cases the results are poor in the upper extremities after cervicodorsal ganglionectomy. Although the good results after sympathectomy have promoted disagreement with Lewis, the bad results make it equally as difficult (though not admitted) to agree with Raynaud.

We believe that Lewis is correct in his contention that Raynaud's disease is primarily and essentially a local vascular disorder for the following reasons.

1. Much of the indictment of the sympathetic system rests on the fact that sympathectomy greatly benefits mild cases. The fact that it does not benefit advanced cases has led some to admit that in these there is a degree of inherently abnormal vasoconstrictor response to cold. Besides, one would not expect much benefit after organic vascular change had taken place. We can see no reason why this entire reasoning could not be changed around. If a local vasospastic disorder exists, the normally superimposed sympathetic influences (response to cold, emotion, etc.) will enhance the abnormality and use up the narrow margin of reserve possessed by the cutaneous vessels. Sympathectomy should be beneficial, and the degree of benefit will be contingent upon the severity of the disease and the magnitude of the vasoconstriction normally imposed on the vessel. Obviously, sympathectomy would give the best subjective and objective results in mild cases, but the results constitute a palliation and not a cure in the strict sense. Furthermore, if the sympathetics were at fault, the results from sympathectomy should be better even in advanced cases.

2. We have recently demonstrated[2] that the inherent capacity of the arterioles to respond to cold is tremendous. If, after unilateral cervicodorsal ganglionectomy, one takes the nude patient into a refrigerator at 0° C., and follows the temperature of the fingers, he will be able to measure quantitatively the magnitude of the peripheral response and that of the central response. After an hour in the refrigerator the temperature of the fingers may have dropped 10 to 18° C., and only 3 to 5° of this is accounted for by the sympathetics.

*We are constrained to wonder how often and to just what degree the beneficial results of sympathectomy are attributed to relief of pain. We have given evidence that the aching, stinging pain incident to the early Raynaud's syndrome or to severe cold[2] is abolished by sympathectomy. Hence adequate cervicodorsal ganglionectomy will result in great subjective benefit, even though it may have little influence on the local progress of the disease. Our first patient, as reported in this paper, based his belief that the result was good purely upon the relief of pain. We believe that many of these afferent (sympathetic) pain-bearing fibers course in the sheaths of major vessels, and that this explains why Leriche[25] succeeded in abolishing the pain in his cases by periarterial sympathectomy. We feel that his evaluation of periarterial sympathectomy must be based largely on subjective relief. Of course if the disease advances to a stage where somatic pain fibers become involved by organic tissue changes, the patient may again suffer pain of a different nature.

We believe that this sympathetic pain incident to severe cold is initiated by marked vasoconstriction, but we do not believe that vasoconstriction is a sine qua non of sympathetic pain. It appears to be the current view that sympathetic pain implies vasoconstriction, and Morton and Scott[11] bring into their discussion such syndromes as amputation stump pain and causalgia as examples of the pain of angiospasm.

3. We have also observed[2] that the effect of cold on the normal hand (local application of ice or an induced central response) is a transient blanching, followed by dilatation of the capillaries. The sympathectomized hand in a refrigerator will exhibit very mild flushing, but nothing to compare with the flush of the normal hand. The flush of the normal hand may later develop a cyanotic hue. The purpose of this capillary dilatation, in combination with arteriolar constriction, is undoubtedly to protect the skin against the lethal effect of cold.* When the first patient (F. C.) reported herein was exposed in the refrigerator, both hands presented islands of pallid skin and the distal two joints of all fingers were blanched. The only difference in the appearance of the two hands was one of degree. The sympathectomized hand was not quite as flushed in the nonblanched zones and not quite as cyanotic as the other hand. Although one could detect this, we doubted whether a color photograph would be able to show the difference. The sympathectomized hand felt warm subjectively and was devoid of pain, but the other hand ached and stung with cold. There was no evidence of regeneration or incomplete sympathectomy. The sweating test showed complete absence of sweating over the left upper extremity and throughout the normal distribution of the inferior cervical and upper two thoracic ganglia. The temperature of all of the fingers on the left (intact) side was significantly higher than that on the right at room temperature, except on one occasion, when the temperatures were almost the same.

Thus, in this case we witnessed a striking example of the effect of sympathectomy on the hand of a patient with Raynaud's disease. It abolished the aching, stinging pain ordinarily produced by cold, but altered the temperature and color changes only to a degree which was in keeping with what would be expected by eliminating a normal sympathetic influence.

4. We should like to call attention to the fact that cold normally causes a transient blanching, followed by flushing of the hand and

*Capillary dilation in response to cold may be a peripheral (first order) response or a central (third order) response, and is normally a combination of the two.[2] After unilateral cervicodorsal ganglionectomy, a small block of ice on the forearm or hand will produce the same phenomenon and to the same degree on both the normal and sympathectomized sides. The effect is first a pallor, and this is followed shortly by reddening limited to the area of application. When the ice is removed, the flush persists for some time. This is a local (first order) reaction. If the patient is taken into a refrigerator, so that the entire body is exposed to cold, the first order reaction will be markedly re-enforced on the normal hand through the agency of central reflexes. The normal hand will become quite flushed, and later may present a cyanotic hue, whereas the sympathectomized hand will become only slightly flushed.

The flushing after local application of cold which was studied by Lewis[26] is a local reaction of the first order. His supplementary studies[27] involved first and third order responses. Lewis found that the reaction was not present, as is true of the histamine flare, after degeneration of peripheral nerves. The reaction was not abolished after degeneration of sympathetic nerves. Lewis therefore attributed the reaction to an axon reflex. Inasmuch as this first order response is not influenced by degeneration of sympathetic nerves, our observation in the refrigerator cannot be attributed to the latter, but constitutes strong evidence for the existence of a central control of capillary dilatation in response to severe cold. The term "central" must for the present include hypothalamic reflexes (third order response) and reflexes through the cord (second order response).

fingers, and that this capillary dilatation is an integrated response which is largely (but not entirely) under the control of central reflexes, probably through the hypothalamus. The hand of the patient with Raynaud's disease, however, becomes excessively blanched when exposed to cold and remains so for a long period of time, so that, if this blanching is a reflex vasomotor phenomenon, we can at least say that it is not in keeping with what we know the normal, integrated, sympathetic response to be. We feel justified in concluding that such observations indicate that the capillaries, as well as the arterioles, are exhibiting an abnormal, local, vasoconstrictor response to cold. This is of such a marked degree that the normally integrated central function cannot be effective in establishing capillary dilatation. The hand of the patient with Raynaud's disease will, after long exposure, go through the red and cyanotic color changes. We feel that a normal hand in the refrigerator differs from the hand of a patient with Raynaud's disease at higher temperatures only in this one respect, namely, that the capillaries of the latter exhibit a sustained constriction.*

5. Lewis[9] has shown that the effects of cooling or warming a single finger of a patient with Raynaud's disease are local and that, if this is a sympathetic reflex, it does not obey the laws which characterize sympathetic reflexes.

SUMMARY

After digesting some of the literature and studying three cases of Raynaud's disease, we feel that the evidence is greatly in favor of the conclusion that the disease is primarily a vascular, and not a sympathetic, disorder. Sympathectomy is beneficial objectively because it eliminates the vasomotor influence which is normal in any given case. It is beneficial subjectively because it abolishes the aching and stinging pain of vasoconstriction. (Whether the relief of this type of pain is brought about by cutting afferent sympathetic fibers or by an alteration in the threshold for pain following the interruption of efferent sympathetics remains unsolved.) Our contention is based largely on the following major considerations: (1) As Lewis has shown, the vascular spasm caused by cold water and its release in warm water are strictly local phenomena. (2) We have demonstrated that, after preganglionic or postganglionic sympathectomy, the hands still retain the local disorder objectively, that is, cold continues to cause the color changes. This objective response is diminished in mild cases, but only to a degree that would be expected after eliminating the normal sympathetic vasomotor influence. (3) When a patient is taken nude into a refrigerator, and kept there long enough to cause a fall in central temperature, and, at

*We cannot agree with Kerr[10] when he states that the pallor has no significance and is entirely artificial. We feel that the role of the capillaries in the vasospasm of Raynaud's disease is quite important and is probably the factor that renders the tissue liable to death.

the same time, one of his hands is kept at room temperature, the latter does not show evidence of vascular spasm, either subjectively or objectively, even though the exposed hand reacts severely. One is justified in assuming that, if the sympathetic system is responsible for the vascular spasm, the hand at room temperature under these circumstances should react somewhat like the other hand.

According to evidence which is only partly presented in this paper, preganglionic sympathectomy in itself does not provide a solution to the problem of the treatment of Raynaud's disease of the upper extremity. After preganglionic sympathectomy the upper extremity is much more comfortable than after cervicodorsal sympathectomy, but the difference is probably the result of trauma incident to removal of the stellate ganglion. We feel that the sympathectomy should be accomplished with a minimum of surgical interference and believe that it is necessary to remove only the second dorsal ganglion in order to completely sympathectomize the upper extremity. Additional data relevant to this point will be presented in another paper.

CONCLUSION

Raynaud's disease is a local disorder of the vascular system and not primarily a disorder of the sympathetic nervous system.

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THE EFFECTS OF THE INGESTION OF EXCESSIVE AMOUNTS OF SODIUM CHLORIDE AND WATER ON PATIENTS WITH HEART DISEASE

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IT IS generally assumed that a restricted intake of salt and water in cases of heart failure is desirable, which implies that unlimited use of salt and water is undesirable. The basis for such an assumption, however, rests largely on theoretical considerations. It was for the purpose of gathering data regarding the effects of increase of salt and water intake on patients with heart disease that this study was undertaken. The effects of increased salt intake and increased ingestion of water were studied separately.

PROCEDURE

Five patients, four of whom had recently recovered from heart failure, were given increased amounts of sodium chloride by mouth. The subjects were first observed while they were on a standard diet which yielded 2,000 calories and contained 62 to 75 Gm. of protein, 250 Gm. of carbohydrate, 80 Gm. of fat, 2,000 c.c. of fluid, and about 5 to 7 Gm. of sodium chloride. Preliminary observations on each patient were continued until a more or less constant state had been reached. This required four to twelve days in the various subjects. Immediately thereafter, in addition to the above diet, 10 to 12 Gm. of sodium chloride, in capsules, were given daily to the point of discomfort. These experimental periods, consequently, were variable, extending from four to fourteen days. Both during control and test periods, all patients were kept absolutely at rest in bed.

The effect of an increased ingestion of water was studied on three patients who had recently recovered from heart failure. (Two of these patients also served for the salt experiments.) During the control observations, the standard diet mentioned above varied in each case only as to its daily fluid content. To one patient, 1,000 c.c. of fluid were given; to a second, 1,500 c.c.; and to a third, 2,000 c.c. In the test period water was added so that the fluid intake was increased to 3,000 c.c. for all.

Of our six subjects, three had arteriosclerotic heart disease, and, when they entered the hospital, were suffering from severe congestive failure. Of these three, two had auricular fibrillation, and the third had delayed A-V conduction. The fourth patient had concretio cordis and auricular fibrillation and entered in a state of severe cardiac insufficiency. The fifth patient had a lesser degree of heart failure, associated with pulmonary fibrosis and pneumoconiosis. On admission, the sixth had rheumatic heart disease involving the mitral and aortic valves, and moderately severe failure. All of the patients except the last were men.

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In each case, daily observations before and during the administration of an increased amount of salt or water were carried out under basal conditions. Oxygen consumption was measured by the open (Tissot) method, or by the closed (Benedict-Roth) method. The respiratory rate and respiratory minute volume (average of a seven-minute period) were measured. The maximum of three attempts was recorded as the vital capacity. The heart rate was counted at the apex, and systolic and diastolic pressures, measured by auscultation, were taken three times within six minutes, and averaged. Frequent electrocardiograms were made. The cardiac area was estimated from a teleroentgenogram with a planimeter, according to the method of Levy.[1] The venous pressure was measured by means of a modified Moritz and Tabora method,[2] and the arm-to-tongue circulation time was estimated by the Decholin method, as described by Winternitz, Deutsch, and Brüll.[3] In addition, the weight of each patient was recorded daily. Sodium and chloride balances were ascertained by chemical analyses of the ingested food and the urine. The daily urinary output of chloride was measured by the method of Volhard and Arnold.[4] Determinations of urinary sodium were carried out upon aliquots from four-day periods, according to the method of Butler and Tuthill.[5] Samples taken from a homogenous mixture of an entire day's food were analyzed for chlorides by the above method. From aliquots of the dry, ashed material from the homogenous mixture of food, sodium was determined by the same technique. The fecal excretion of sodium and chloride was not measured. Urinary nitrogen was determined by the method of Folin and Denis.[6]

RESULTS

Salt Experiments.—As might be expected, there were individual variations, but the case presented in detail below will serve to illustrate the type of reaction which can be anticipated under the conditions of our experiments.

Fig. 1 illustrates the daily observations on a patient with arteriosclerotic heart disease and auricular fibrillation. There was a control period of twelve days, during which the patient received the basic diet containing 121 meq. (2.8 Gm.) of sodium, and 140 meq. (5.0 Gm.) of chloride. During the next period 10 Gm. of sodium chloride were added daily to the basic diet.* The intakes of sodium and chloride during this interval of increased salt administration were 289 meq. (6.6 Gm.) and 299 meq. (10.6 Gm.), respectively. This period had to be terminated in six days because of the alarming condition of the patient. During the next four days he received only the basic diet. At the end of this time, while he was still on the same diet, he was digitalized. Digitalis leaf in a dose of 0.6 Gm. daily was given for three days, then 0.2 Gm. daily for three days, followed by a maintenance dose of 0.1 Gm. for the remainder of the experiment. On the fifth day of digitalization, 10 Gm. of salt in capsules were again given daily, and continued for fourteen days. The intake of sodium and chloride during this final period was identical with that of the first high-salt period.

*Because of a change in brands of food at this time, the sodium content of the basic diet was found to be 118 meq., and the chloride, 128 meq. These values hold from the end of the control period to the end of the experiment.

The heart rate, which was irregular, but averaged about 80 per minute in the initial twelve-day period, gradually increased during the first five days of high-salt intake to 90 or more. In the next twenty-four hours the heart rate rose sharply to 135 per minute. Following an

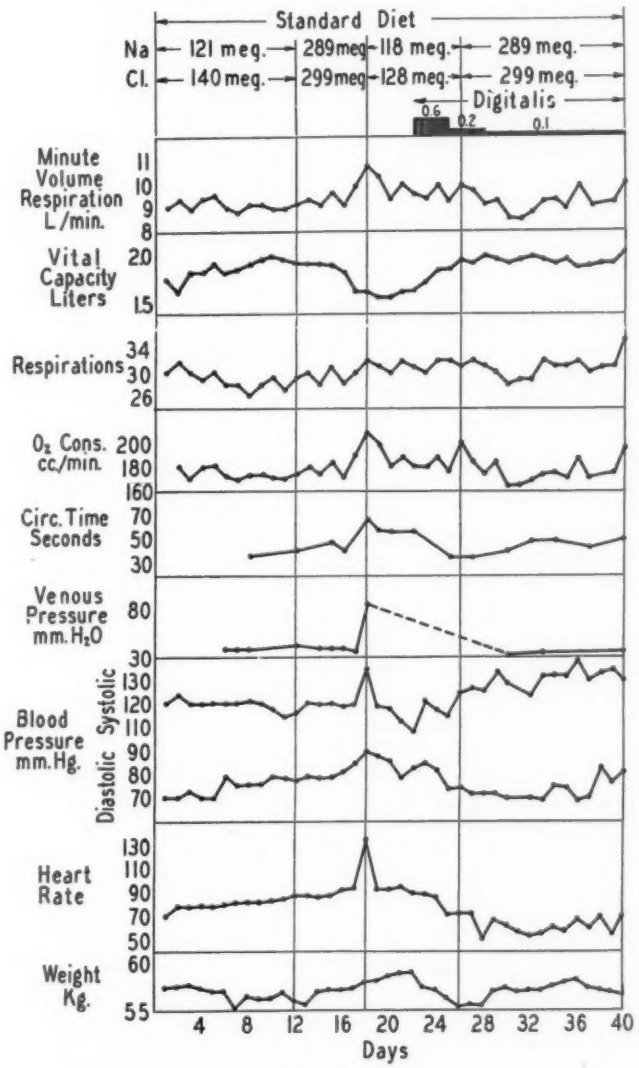

Fig. 1.

initial, rapid fall in rate after withdrawal of the excess of salt, the rate decreased gradually until digitalization was attained, when a more rapid decline set in, resulting in a fall to a level below the initial one. This improvement was maintained in spite of the second period of salt administration, although the rate showed a tendency to rise in the latter portion of this interval. In other words, there was an acute, alarming

rise in heart rate after six days of increased salt intake without digitalis, but, after the patient was digitalized, the same daily amount of salt failed to produce any marked response at the end of fourteen days.

The systolic blood pressure exhibited an acute rise of 15 mm. Hg. above the control level on the sixth day of salt administration. Immediately after withdrawal of the extra salt, the pressure fell below the initial level. However, with the administration of digitalis, the curve rose steadily in the second period of increased salt intake and reached a plateau above the control value. The diastolic pressure also increased about 15 mm. Hg at the end of the first high-salt period, but fell steadily during the administration of salt and digitalis to a level below the control value. There was, therefore, during the digitalis period, a striking increase in pulse pressure.

The venous pressure followed a course similar to that of the heart rate. During the initial control period and the first five days of the subsequent period of increased salt intake, readings of 40 mm. of water were obtained consistently. On the sixth day of the latter period a sudden rise to 90 mm. occurred. During the administration of extra salt and digitalis, however, the venous pressure remained slightly below the level of the control period.

On the sixth day of increased salt administration there was a sudden increase in the arm-to-tongue time from forty to sixty-five seconds. This tended to diminish slowly during the subsequent four days on the basic diet. With digitalization, the circulation time fell to forty seconds. In the latter part of the subsequent period of increased salt feeding and digitalis administration, the circulation time tended to rise gradually to fifty seconds.

The respiratory rate was rather irregular during the whole experiment. However, salt feeding, with or without digitalis, produced, in general, a slight rise.

During the control period the vital capacity was quite constantly between 1.8 and 1.9 L. Toward the second half of the subsequent salt period the readings fell gradually. The decline continued even after the excess salt had been withdrawn. A total decrease of 400 c.c. was observed at this time, which represents a significant change of 21 per cent. With the institution of digitalis therapy, the vital capacity returned to the initial control value, at which level it remained in spite of subsequent high-salt feeding.

The respiratory minute volume increased sharply toward the end of the first salt period to about 1.75 L. over the average control value. Withdrawal of the salt was followed by an immediate, but only partial, improvement. Digitalization produced a further improvement, but, with the administration of extra salt again in the final period, the values showed a tendency to rise.

The curve of oxygen consumption followed closely that of the respiratory minute volume. There were a marked rise during salt feeding without digitalis and improvement early in the course of digitalization, followed by a tendency to rise when increased amounts of salt were again given.

With the exception of the vital capacity, the maximal changes for all the factors observed occurred on the sixth day of the period of increased salt feeding without digitalis. This was not true of body weight. Although it increased by 1.5 kg. at this time, it continued to rise another 1.5 kg. four days after the extra salt had been withdrawn. Possibly it would have risen further, but for the administration of digitalis at this time, which resulted in a rapid loss of 4.0 kg. With the readministration of excess salt during digitalization the weight rose somewhat, but never attained the previous peak. Since the patient was in nitrogen balance during the experiment, these weight changes represented fluctuations in body water. Water balance studies from the urinary volume alone were impossible because of the appreciable but unascertainable loss by sensible and insensible perspiration.

Roentgenologic examination showed a slight increase in the size of the heart on the sixth day of excessive salt intake; the surface area increased from 174 sq. cm. to 180 sq. cm. The roentgenogram also showed some increase in the degree of pulmonary congestion and slight right-sided hydrothorax. After digitalization the heart size decreased to 158 sq. cm., the pulmonary fields appeared more radiant, and the pleural effusion receded.

Electrocardiograms showed no appreciable changes.

TABLE I

SODIUM BALANCE DURING INCREASED SALT INTAKE

PERIOD	DAYS	DAILY Na+ INTAKE (MEQ.)	AVERAGE DAILY URINE Na+ OUTPUT (MEQ.)	AVERAGE DAILY DIFFERENCE (MEQ.)	CORRECTED BALANCE (MEQ.)	TOTAL ESTIMATED BALANCE (MEQ.)
Standard	12	121	88	+ 33	+13	+156
Increased salt	6	289	182	+107	+87	+522
Standard	4	118	151	- 33	-53	-212
Standard and digitalis	4	118	183	- 65	-85	-340
Increased salt and digitalis	14	289	226	+ 63	+43	+602

Balance studies of sodium from measurements of the intake and urinary output revealed definite retention during periods of excess salt intake. The changes from period to period are presented in Table I. An average daily retention of 33 meq. apparently occurred during the control period. In the subsequent period of increased salt intake, the average daily retention was 107 meq. In the following four days on

the basic diet alone, an average loss of 33 meq. per day was encountered; and 65 meq. per day of sodium were excreted during four additional days on the basic diet and digitalis. A retention averaging 63 meq. per day occurred during the final fourteen days of high salt feeding and digitalis.

The course of sodium metabolism from period to period appears even more significant when the figures are corrected for the loss of sodium through other channels. Studies of insensible perspiration in normal persons show that the amount of sodium thus lost is independent of the intake and is usually close to 10 meq. per day.[7, 8] Furthermore, according to the literature,[9] as well as unpublished results obtained in our laboratories, fecal sodium, regardless of the amount ingested, is also fairly constant at 10 meq. daily.

In a group of six cases studied by us in which body weight became stationary during the control periods and the daily urinary output of sodium had reached a constant level, i.e., sodium and water equilibrium, the average difference between intake and urinary output was 22 meq. Thus, under ordinary conditions, one may consider that about 20 meq., in addition to the urinary output, represents a fair estimate of the total loss of sodium. By subtracting this amount from the observed retention, we constructed the sixth column in Table I to record "corrected sodium retention," in order to obtain a better approximation of the sodium metabolism during the course of the experiment. Thus, the total retention for the twelve-day control period was 156 meq., which is only 13 meq. per day. During the subsequent period of increased salt intake, the total retention in six days was 522 meq., or 87 meq. daily. During the following eight days on the basic diet, including four with digitalis administration, a total of 552 meq. was lost. The final salt period, with digitalis administration, revealed a retention of 602 meq. in fourteen days, or 43 meq. per day.

The total quantity of urinary chloride excretion during a four-day period was higher, as expected, than that of sodium. However, the changes of both from period to period were found to follow almost the same slopes, e.g., the degree of chloride retention closely approximated that of sodium, and need not be further elaborated.

Water Experiment.—Fig. 2 presents the observations in a typical experiment. The patient, a woman who had rheumatic heart disease with mitral stenosis and regurgitation and aortic regurgitation, had recently recovered from an attack of heart failure.

As a control, a standard diet containing 115 meq. (2.6 Gm.) of sodium, 135 meq. (4.9 Gm.) of chloride, and 2,000 c.c. of fluid was administered for twelve days. At the end of this time, when her condition had become stabilized, the fluid intake was increased to 3,000 c.c., but no changes were made in the diet. This amount of fluid represented an uncomfortably high intake for the patient. In other words, fluids were liter-

ally forced. This was maintained for eight days. During the next four days the fluid intake was diminished to the initial control level of 2,000 c.c.

During the first twelve days she improved, and her body weight, systolic pressure, respiratory rate, and vital capacity rapidly became stabilized. The heart rate, diastolic pressure, and basal metabolic rate decreased slightly. This trend can be fairly attributed to the bed rest.

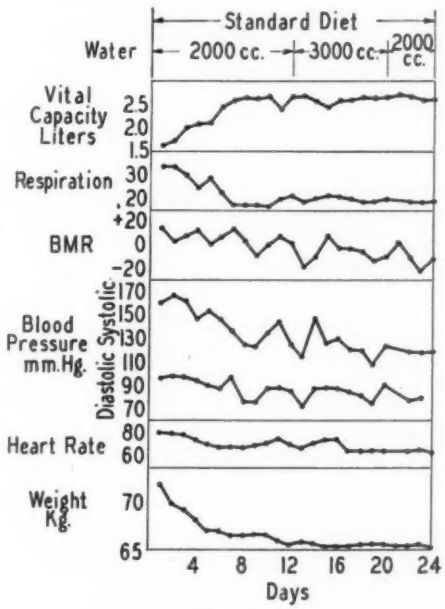

Fig. 2.

During the period of high water intake, the heart rate and basal metabolic rate tended slightly further toward normal, but everything else remained unchanged. The last four control days were likewise uneventful. The results were the same in the other two experiments, no matter whether the increase of fluid intake to 3,000 c.c. represented an additional 1,000 or 2,000 c.c. of water.

DISCUSSION

Increased water ingestion, as such, was apparently harmless. It should be noted that the level of salt intake in this experiment was average (2.6 Gm. of sodium, representing 6.6 Gm. of sodium chloride), and therefore this conclusion applies to a normal intake of salt. On the other hand, raising the sodium chloride intake (about 17 Gm.) produced ill effects upon the circulatory status, namely, a clinical picture which was indistinguishable from that of congestive heart failure. Comparison of the experiments with increased salt intake suggested that, in gen-

eral, the intensity of harmful effects was proportional to the degree of salt retention. This fact may account, in part, at least, for the individual variations noted.

The question arises whether the increased salt intake produced true heart failure. Actually, what is regarded as heart failure is essentially a condition in which there is an increased and more slowly circulating blood volume. It is, of course, theoretically possible that conditions other than heart failure may be accompanied by such a circulatory state. However, in view of the underlying cardiac disease and a history of previous failure, it is logical to assume that the condition we observed was, in fact, heart failure. In any event, it was indistinguishable from heart failure. In this connection it should be noted that, shortly after the turn of the century, Vaquez and Digne[10] were likewise impressed by bedside observations of recurrent heart failure after the administration of salt to patients whose heart disease had shown considerable improvement with rest in bed and a Karell diet (1.5 Gm. of sodium chloride).

The discussion thus far has tended to place emphasis on the effect of an increased sodium *intake* on patients with heart disease. Our results indicate that the emphasis should rather be placed on the degree of sodium *retention*, for, unless there is a significant and fairly rapid retention, no signs of heart failure appear. In other words, evidence of heart failure may be produced fairly easily by a moderate intake of sodium chloride when conditions favor sodium retention, although a great increase of sodium chloride intake may produce no ill effects when there is little or no sodium retention, as, for example, under the influence of digitalis or diuretics. The extent of salt restriction which is necessary to obviate retention in cases of heart failure is therefore variable. Since it is not practicable to ascertain this amount, and since retention must vary in the same patient from time to time, it would appear wise simply to reduce the salt intake to a minimum.

Among other factors which favor sodium retention acute infections may be mentioned. It is generally known that pneumonia causes chloride retention (and presumably sodium retention). It is not as well known that simple upper respiratory infections may likewise produce a significant degree of sodium retention. One of our patients contracted an acute upper respiratory infection in the course of an experiment, so that we had an unexpected opportunity to observe the effect upon sodium metabolism. Because such data can be obtained only by chance, and because they have a bearing upon our problem in general, we report the results in detail. Early in the control period, while the patient had moderate heart failure, there were a rapid loss of weight and a negative sodium balance, associated with nitrogen equilibrium. According to the work of Gamble, Ross, and Tisdall,[17] the constancy of the electrolyte concentration of body fluids allows one to approximate changes in

water balance by means of the content of base in the urine. Therefore, since 1 kg. of extracellular fluid contains 140 meq. of sodium, a loss of body weight of 1 kg., associated with a negative balance of this amount of sodium, indicates a loss of approximately 1 kg. of extracellular water. In Fig. 3 the daily cumulative changes in sodium balance and body weight are compared with each other by representing along the ordinates 1 kg. equivalent to 140 meq. of sodium. It is thus apparent that, during the first four days, at least, the loss of weight was due almost entirely to loss of extracellular fluid. On the seventh day the patient developed a sore throat and fever. Thereafter, the sodium balance studies revealed marked retention, in spite of a further slight loss of weight (Fig. 3). By the twelfth day (the nineteenth day of the experiment) after the onset of the infection, although the sodium lost initially had been entirely regained, the body weight was diminished by 4 kg. In other words, retention of sodium occurred without a concomitant gain of body water. At this time the patient was taking extra fluids. That this course of events cannot be attributed in some way to the forcing of fluids is indicated by the absence of sodium retention in the other experiments in which fluid was forced. By a similar coincidence, Mackay and Butler[9] also found sodium retention (daily average of 37 meq.) without concomitant water retention during an acute upper respiratory infection in a normal subject. In our case the daily average sodium balance preceding the infection was –24 meq. During the infection there was a daily average retention of 34.5 meq. of sodium.

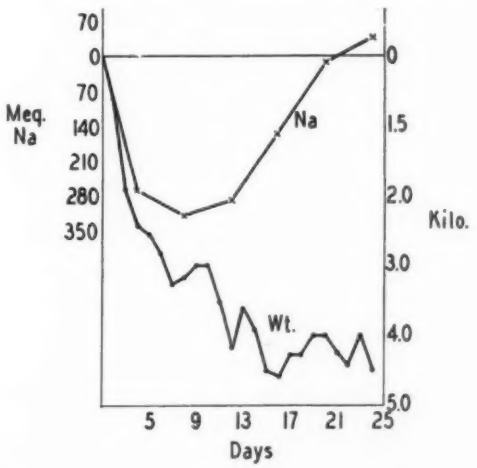

Fig. 3.

It is a common observation that the onset of heart failure in patients with heart disease is often preceded by an acute upper respiratory infection; the implication that the accompanying sodium retention may be an important precipitating factor is evident. Therefore, it seems worth

while to give a cardiac patient diuretics if he develops an upper respiratory infection. Such a procedure has appeared to be beneficial in some of our cases.

It is of interest to speculate on the mechanism involved in the relationship between sodium retention and heart failure. One possible explanation for this retention is that it results from inability of the kidneys to excrete sodium because of passive congestion. It will be recalled that in the high salt experiment, following digitalization after the initial increase in salt intake, the degree of improvement of the circulatory status was greater than in the preliminary control period. Some degree of passive congestion may therefore be postulated in our patients, who, though improved, were not fully recovered from the heart failure before the extra salt was given. With sodium retention there may be an increase of plasma volume. The consequent increase in circulating blood volume may therefore conceivably place an additional strain on an already weakened heart. This, in turn, results in greater renal congestion, thereby setting up a vicious circle. This circle can be broken either by factors which tend to strengthen the heart or decrease its work (rest, digitalis, sedatives), or act directly upon kidney function (diuretics).

Our results may be ascribed to an increase in the sodium content of the heart muscle, as suggested by Wilkins and Cullen.[11] These authors found from chemical analyses of normal hearts and hearts of patients who died of cardiac failure that, in the latter, the water and sodium content was elevated and the potassium content diminished. They therefore concluded that a disturbance in the relative concentrations of these electrolytes might underlie the mechanism of cardiac failure. However, proper recalculation of their results reveals that the differences in water, sodium, and potassium between the two groups could be entirely accounted for by a rise in the extracellular water content, i.e., edema fluid. Hence, since their observations could readily be explained by secondary edema of the heart muscle, it is unjustifiable to assume that the change in electrolytic content is the cause of failure of the heart muscle.

It is possible that acute and severe sodium retention may produce the clinical manifestations of heart failure even in the absence of previous heart disease. Reid and Teel[12] reported the appearance of acute heart failure in two patients with toxemia of pregnancy. Ferrebee, Ragan, Atchley, and Loeb[13] reported similar changes in patients with Addison's disease after overdoses of desoxycorticosterone, associated with an increase of plasma volume. Wilder[14] observed acute heart failure with a low-potassium and high-sodium diet and desoxycorticosterone. In acute nephritis, similar changes may supervene.[15] In these conditions, what is apparently heart failure may well be associated with acute sodium retention, leading to a rapid increase in circulatory blood volume, but without underlying cardiac weakness. However, it is quite pos-

sible that, in such cases, we are dealing not with true heart failure but with a circulatory condition clinically indistinguishable from heart failure.

As to the effect of increased water intake, there would appear to be no sound theoretical reasons why such an increase should be harmful. This is true at least of an increase in fluid intake to such an amount as patients with heart disease might spontaneously take without too great discomfort. Since the kidney offers no barrier to the excretion of water itself, and since no retention is possible without an equivalent supply of sodium and chloride, there is no reason why water could not be reasonably easily eliminated. Since there is only a transient rise, and that of small degree, in cardiac output after the ingestion of as much as 1,000 c.c. of water in a few minutes,[16] there is little added strain upon the heart. The ingestion of ordinary amounts of water, therefore, would be expected to be harmless.

SUMMARY

1. In patients who are recovering from heart failure, a moderate increase in the ingestion of sodium chloride may produce, within four to eight days, a clinical picture which is indistinguishable from that of congestive heart failure. Such an effect is obviated by digitalization.

2. Under similar conditions, an increase to 3,000 c.c. in the daily intake of water for as long as eight days results in no measurable or noticeable harmful effects.

3. The harmful effects of an increase in the intake of sodium chloride are apparently related to the degree of sodium retention, rather than the increased intake as such.

4. The possible mechanism of sodium retention is discussed.

5. It is suggested that, since there is a significant degree of sodium retention during upper respiratory infections, the latter may play a role in the oft-observed relationship between infection and the precipitation or aggravation of heart failure.

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Maude E. Abbott
1869-1940

Maude Abbott died more than a year ago, in the fall of 1940. She is still sorely missed by her many friends, and will be missed throughout the lives of those who knew her.

Here and there appeared brief tributes and biographical notes soon after her death, and a memorial meeting to her was held in October, 1940, in Boston, by the New England Heart Association. Abstracts of some of the addresses given at that meeting were published in the McGill Medical Journal in October, 1940 (Vol. X, p. 28), as was a list of Maude Abbott's books and papers on cardiovascular disease prepared by Donald Bauer. To bring the most pertinent quotations and the useful bibliography to the readers of the American Heart Journal, it has been suggested that the present note be published.

The first article of the series in the McGill Medical Journal was by Dr. Charles F. Martin, Emeritus Dean of Medicine, McGill University. His opening words were as follows:

"Doctor Maude E. Abbott was buried in the churchyard of her little native town of St. Andrews by the side of her forebears, and among the flowers and trees she loved so well—a simple, quiet burial, as if the life just ended had been like a thousand others. She was as consistently humble in the realm of the dead as in life.

"A few hours previously, at a service in Montreal, the English cathedral had been crowded by members of the faculty and the teaching staff, medical students, and hundreds of citizens who came to pay her homage, because they loved her.

"In this manner was closed the life chapter of a scholar at McGill who, with but few exceptions, had greater international repute and contacts than anyone in the Canadian profession."

The next paper, by Dr. Paul D. White, of Boston, concerned Maude Abbott's contributions to cardiology. The following paragraphs were the opening and closing ones.

"Maude Abbott's very first paper entitled 'So-Called Functional Heart Murmurs' gave evidence of her absorbing interest in cardiology from the earliest days of her medical career. This paper was published in the Montreal Medical Journal in 1899 and was based on the records of 466 patients with murmurs encountered on the wards of the Royal Victoria Hospital in the years from 1895 to 1898 while Maude Abbott served as graduate student there in clinical medicine and in pathology following her return from two years of study in Europe which in turn

followed her graduation in medicine from Bishop's College in 1894. Dr. Abbott at the outset credited Dr. Charles F. Martin with the suggestion that she undertake this study, and it is a great pleasure for those of us who have had the privilege of counting both these medical leaders as friends to learn that the life-long collaboration between them was so evident in these early days.

"This interesting and useful paper on 'So-Called Functional Heart Murmurs' is worth reading today. Dr. Abbott pointed out that 'functional' pulmonary and mitral systolic murmurs are common in anemia, fevers, and certain toxic states, and that even diastolic murmurs may not have an organic origin in the fashion of deformity of the valves themselves.

"During the next year, 1900, in the Philadelphia Medical Journal, doubtless as the result of Sir William Osler's advice, Maude Abbott published a note on a specimen showing a small saccular aneurysm and an accessory branch of the right renal artery. At this time Maude Abbott was reviewing and cataloguing Sir William's museum specimens left at McGill and came across a unique case of malformation of the heart described originally by A. F. Holmes in the Transactions of the Edinburgh Medico-Chirurgical Society for 1824. Maude Abbott republished this article in the Montreal Medical Journal in 1901 and this case along with others with congenital defects of the heart laid the foundation of her interest in congenital heart disease which steadily mounted from that time on under the stimulus of Sir William Osler with whom she frequently conferred. Being aware of her experience in this subject and believing that she was already a leader and perhaps the leader on this side of the water in this field, Sir William asked her to write the section on congenital cardiac disease in his System of Modern Medicine, Its Theory and Practice, prepared with Thomas McCrae and published by Lea and Febiger in 1908."

"The Clinical Classification of Congenital Heart Disease in 1924 supplemented by the article in the Lancet in 1929 presented the very practical division that she made of patients with congenital heart disease into the acyanotic and the cyanotic groups with which the world is now familiar and which has come to be currently accepted. Perhaps this along with the final tabular analysis of 1,000 cases is Dr. Maude Abbott's chief contribution to cardiological literature.

"However, when we review Maude's Abbott's influence in the field of cardiovascular disease we find that far more important than any of her written works was her vital stimulus to others. Her spirit was indefatigable. She inspired innumerable other workers throughout the world and was always very willing, in fact eager, to place at the disposal of anyone who sought it, her own vast experience and the details of pathological and clinical findings in the cases she had studied herself or analyzed in the literature.

"Thus it may be said that many of the contributions, sometimes very important, to our knowledge of congenital heart disease made by others, are due directly to Maude Abbott's influence. What little has been accomplished in the field of congenital heart disease by our own group at the Massachusetts General Hospital can be traced in major part to our acquaintanceship with Maude Abbott. She was an inspiration to us all, pathologists and clinicians alike. Her presence acted as a ferment and yet the most pleasant sort of a ferment. She often started controversies, but there was never anything that was disagreeable about any of them, for her personality, generosity, and friendship were of the very highest type. Cardiological literature will miss her, but the living medical world as such will miss her still more. Thus, it is not simply as the world's authority on congenital heart disease that Maude Abbott will be missed and best remembered but as a living force in the medicine of her generation. Hers was a great spirit."

Then came the paper by William Boyd, of Toronto, on Maude Abbott and medical museums. It began as follows:

"It is difficult for anyone connected with the International Association of Medical Museums to believe that Maude Abbott is dead, or to picture that association without the vivifying stimulus of her enthusiasm. At the very first meeting in Washington on May 15th, 1907, she was elected secretary-treasurer, a post which she held until her death, and I suspect that it was mainly due to her that the association came into being. She acted as editor of the bulletin of the association from 1907 to 1938. The international aspect of the association was particularly dear to her heart, although at times she found it none too easy to get her fellow-members on the council to share her enthusiasm. It is interesting to note that by the time of the second meeting the following officers had been elected: President: Prof. W. G. MacCallum, of Baltimore (a graduate of Toronto); First Vice-President: Prof. Sims Woodhead, of Cambridge; Second Vice-President: Prof. James Ritchie, of Edinburgh; Third Vice-President; Prof. Ludwig Aschoff, of Freiburg, Germany, whilst Prof. J. G. Adami, at that time Professor of Pathology at McGill, was on the Editorial Board of the Bulletin. The formation within recent years, entirely as the result of her efforts, of a British section of the association, was a source of special pleasure to her. Unfortunately the days of indiscriminate internationalism are gone for the present.

"The first time that I attended a meeting of the International Association of Medical Museums was over twenty years ago. It did not take me long to discover that the prime mover in the association, the mainspring of its energy, was Maude Abbott. For many years since then I have had the opportunity to observe the part which she has played in the life of the association. A meeting of the association

without 'Maude' as the central point round which everything revolved would be like witnessing the play of Hamlet without the Prince of Denmark."

Dr. W. W. Francis, Osler Librarian at McGill University, wrote of Maude Abbott—Hero-Worshiper:

"One of Maude Abbott's most precious possessions was a holograph letter which reads as follows:

13 Norham Garden,
Oxford, Jan. 23, '08.

Dear Dr. Abbott,

I knew you would write a good article but I did not expect one of such extraordinary merit. It is by far and away the very best thing ever written on the subject in English—possibly in any language. I cannot begin to tell you how much I appreciate the care and trouble you have taken, but I know you will find it to have been worth while. For years it will be the standard work on the subject and it is articles of this sort—and there are not many of them—that *make* a system of medicine. Then too the credit which such a contribution brings to the school is very great.

Many, many thanks!

Sincerely yours,

(signed) Wm. Osler.

P.S.—I have but one regret, that Rokitansky and Peacock are not alive to see it. Your tribute to R. is splendid. My feelings were the same when I read the monograph.

"It refers, of course, to her celebrated monograph, 'Congenital Cardiac Disease' in vol. 4, 1908, of the first edition of Osler and McCrae's 'System,' more widely but less happily known on this side of the water by the ephemeral, salesmanish title, 'Modern Medicine,' on which its American publishers insisted. Such a letter, obviously sincere, was not only a laurel wreath and a passport to fame, but an incentive to even better work if possible. She was again deeply touched when we discovered, only last year, that Osler had inserted a photo of her in his own copy of that volume on the page opposite the beginning of the monograph."

Helen McCurchy, of Toronto, and Elizabeth MacKay, William C. Gibson, and Donald deF. Bauer, of Montreal, ended the series of papers with tributes to Maude Abbott, especially as a teacher. Gibson's own experience was very illuminating:

"When I was a student in first year medicine here in 1933, I began a study of a set of little memo books in the Osler Library which were used by Sir William for jotting down all manner of quotations and case histories. One day a heavy, grey-haired woman came into the Library where I was working, and recognizing the Osler notebooks, asked me if I were an out-of-town researcher in medical history. I replied that I was a first year student at McGill and was interested

in Osler. That was my fatal mistake! I was at once whisked downstairs by this bustling human dynamo who seemed only to cling to the stair rail, letting her feet find the steps if they could. Within a few minutes I was in the midst of a sea of charts, books and pictures. A new edition of the Osler Bibliography was about to be born—but first, 'some medical student with spare time' must be found to help 'with a few simple details.' I was the simple medical student, and the innocent details of the Bibliography haunted my slumbers for the next five years. I walked out of her book-laden office wondering to myself, 'What have I put my foot into now?' What a naive idea! I was soon to be utterly immersed in the sea of Osler's myriad publications, ranging from tapeworms to nurses' education. We would have bouts of activity periodically, trying to classify Osler's papers into a few large divisions such as Natural Science, Pathology, Clinical Medicine, Literary and Educational papers.

"When I went off to Oxford in 1935 I pleaded that the broad expanse of the Atlantic Ocean would make it difficult to continue work on the Bibliography. Not at all! Dr. Abbott was sure that the Oslerian atmosphere of Oxford would contribute enormously to the success of the work. So I wearily trundled several copies of an earlier bibliography over to England for the time-consuming preparation of an index to Osler's contributions. I lived over a tea-room and appropriated 26 cream pitchers from the landlady, one for each letter of the alphabet. I cut up the old bibliographies into strips each bearing a single item, and had no sooner got most of them into their respective jugs than a new maid on the premises threw them all out. Finally, when Dr. Abbott wrote as if she might come over and scalp me as a low grade procastinator, I set to work to paste the items for the the index on a long roll of narrow-gauge wallpaper, and after three days of nothing but glue and tea I got the enormous bundle off to Montreal.

"Never have I heard such rejoicing. 'Maudie' wrote ecstatically about the large consignment of wallpaper and she confided that the new Osler Bibliography was near term. It finally appeared in 1939."

The set of contributions closes with the list of Maude Abbott's publications on cardiovascular disease.

MAUDE ABBOTT'S PUBLICATIONS ON CARDIOVASCULAR DISEASE

1. On so-called functional heart murmurs.
Montreal Med. J. 1899, 28:1-13
Read by Dr. James Stewart to Montreal Medico-Chirurgical Society November 21, 1898, leading to Dr. Abbott's election as the first woman member.

2. Note on specimen showing a small saccular aneurysm on an accessory branch of the right renal artery.
Philadelphia M. J. 1900, 6:959-60

3. Museum notes (report of a case published by A. F. Holmes in the Trans. Edinburgh Med.-Chi. Soc., 1824).
   Montreal Med. J. 1901, 30:522-33; also: R. C. Kirkpatrick, Montreal, 1901, 11p. 4 pl.
   Three-chambered heart identified by Osler as that presented to the Edinburgh group by the first Dean of the McGill Medical Faculty.*
4. Congenital Cardiac Disease.
   in: Modern Medicine (Osler & McCrae)
   Lea & Febiger, Phila. & New York, 1908, 4:323-425
   2nd edition, 1915, 4:323-448
   3rd edition, 1927, 4:612-821
   Of which article Osler wrote: "I knew you would write a good article but I did not expect one of such extraordinary merit. It is by far and away the very best thing ever written on the subject in English—possibly in any language."
5. Statistics of congenital cardiac disease (400 cases analyzed).
   J. Med. Research, 1908, 19:77-81
   Herein was begun Dr. Abbott's celebrated "chart." Cf. items: 4, 6, 39.
6. A chart for the study of congenital cardiac disease.
   Montreal Med. J., 1908, 37:170-3
7. Report of an unusual case of congenital cardiac disease, defect of the upper part of the interauricular septum (persistent ostium secundum), with, for comparison, a report of a case of persistent ostium primum.
   (with Joseph Kaufmann, M.D.)
   J. Path. & Bact., Cambridge, 1910, 14:525-35
8. Patent ductus arteriosus with acute infective pulmonary endarteritis.
   (with W. F. Hamilton, M.D.)
   Tr. Ass. Am. Physicians, 1914, 29:294-308
   Summary of 10 other cases from the literature is included.
9. Reversed torsion of the human heart.
   (with F. T. Lewis, M.D.)
   Anat. Record, 1915, 9:103-5
10. Congenital pulmonary atresia with perforate interventricular septum in a patient aged nine years and six weeks.
    (with S. B. Wolbach)
    Internat. A. M. Museums Bull., 1915, 5:125-9
11. Two cases of widely patent foramen ovale.
    Ibid., 1915, 5:129-34
    Specimens and lantern slides shown to Montreal Medico-Chirurgical Society and the discussion which followed was printed in: C.M.A.J. for October, 1915.
12. On the differentiation of two forms of congenital dextrocardia.
    (with J. C. Meakins, M.D.)
    Ibid., 1915, 5:134-8
13. Double monster of janus type: cephalothoracopagus monosymmetros cyclops synotus.
    (with Joseph Kaufmann, M.D.)
    Ibid., 1916, 6:95-101
14. Reversed torsion of the ventricular bend of the embryonic heart in the explanation of certain forms of cardiac anomaly.
    (with F. T. Lewis, M.D.)
    Ibid., 1916, 6:111-15

*The Osler Memorial Number of the C. M. A. J., 1920, 10: 91-102 "The Pathological Collections of the late Sir William Osler."—Maude Abbott.

15. On the difference between the carbon-dioxide tension in the arterial and venous blood as a diagnostic sign in cardiac septal defects.
(with Walter M. Boothby, M.D.)
Ibid., 1916, 6:122-6

14. Foetus holoacardius acormus in heterologous (triplet) pregnancy.
(with G. W. Phelan, M.D.)
Ibid., 1916, 6:107-11

17. The irritable heart of soldiers and the Hampstead heart hospital.
Ibid., 1918, 7:166-74
The editorial note by A. S. Warthin and the bibliography are noteworthy.

18. Clinical and developmental study of a case of ruptured aneurysm of the right anterior aortic sinus of Valsalva, leading to a communication between the aorta and the base of the right ventricle, diagnosed during life.
Contributions to Medical and Biological Research (dedicated to Sir William Osler, in honour of his seventieth birthday, July 12, 1919, by his pupils and his co-workers).
Paul Hoeber, New York, 1919, 2:899-915

19. Rare cardiac anomaly: cor triloculare biventriculare in mirror-picture dextrocardia with persistent omphalo-mesenteric bay, right aortic arch and pulmonary artery forming descending aorta.
(with Bret Ratner, M.D., and W. W. Beattie, M.D.)
Am. J. Dis. Child., 1921, 22:508-15

20. Parasitic thoracopagus with cardiac anomaly in the host (cor biatriatrum triloculare, transposition of arterial trunks and patent ductus arteriosus).
(with W. F. Watton, M.D.)
Internat. A. M. Museums Bull., 1922, 8:165-76

21. Cardiac defects in the light of the comparative anatomy of the vertebrate heart.
(with Eleanor Shanly, M.Sc.)
Ibid., 1922, 8:188-213

22. Differential study of a case of pulmonary stenosis of inflammatory origin (ventricular septum closed) and two cases of (a) pulmonary stenosis and (b) pulmonary atresia of developmental origin with associated septal defect and death from paradoxical cerebral embolism.
(with D. S. Lewis, M.D., and W. W. Beattie, M.D.)
Am. J. Med. Sc., 1923, 165:636-59
With an historical summary of paradoxical cerebral embolism.

23. Cyanosis (review of an article by C. Lundsgaard and D. Van Slyke in: Medicine, 1923, 2:1-76).
C. M. A. J., 1923, 8:601-4
The Van Slyke technique is hailed as an epoch-making achievement paralleling in physiology the pathological contributions to congenital heart disease of Rokitansky.

24. Treatment of congenital cardiac disease.
in: Blumer-Billings-Forscheimer System of Therapeutics, 3rd. ed.
Appleton & Co., New York, 1924, 4:322-62

25. New accessions in cardiac anomalies. I—Pulmonary atresia of inflammatory origin. II—Persistent ostium primum with mongolian idiocy.
Internat. A. M. Museums Bull., 1924, 10:111-16

26. The clinical classification of congenital cardiac disease.
(with W. T. Dawson, M.A.)
Internat. Clin., 1924, 4:155-88
also: 75th Anniversary Volume of the Women's Medical College of Pennsylvania, 1925, pp. 11-56

27. On the incidence of bacterial inflammatory processes in cardiovascular defects and on malformed semilunar cusps.
Ann. Clin. Med., 1925, 4:189-218
Conclusions based on analysis of "a total of 680 cases charted to date."

28. Multiple associated anomalies.
(with M. Lichtenwald-Myers, M.D., and Margaret Dalsell, M.D.)
Proc. Path. Soc. of Phila., 1925, 27:22

29. The diagnosis of congenital cardiac disease.
in: Blumer's Bedside Diagnosis
W. B. Saunders Co., Philadelphia, 1928, 2:353-514

30. Coaretation of the aorta of the adult type: complete obliteration of the descending arch at insertion of the ductus in a boy of fourteen.
(with W. F. Hamilton, M.D.)
Am. Heart J., 1928, 3:381-421

31. Coaretation of the aorta of the adult type: statistical study and historical retrospect of 200 recorded cases, with autopsy, of stenosis or obliteration of the descending arch in subjects above the age of two years.
Ibid., 1928, 3:574-618
Noteworthy bibliography of 255 items.

32. Double aortic arch and pulmonary atresia, with pulmonic circulation maintained through persistent left aortic root, in a man aged 29.
(with Digby Wheeler, M.D.)
C. M. A. J., 1928, 19:297-303

33. Interventricular septal defect with dextroposition of aorta and dilatation of the pulmonary artery terminating by cerebral abcess.
(with E. A. Baumgartner, M.D.)
Am. J. Med. Sc., 1929, 177:639-47

34. Mirror-picture dextrocardia, complicated by mitral aplasia and pulmonary hypoplasia, with great hypertrophy of the transposed "right" chambers.
(with W. Moffatt, M.D.)
C. M. A. J., 1929, 20:611-16

35. Bicuspid aortic valve of congenital origin with associated defect of the interventricular septum and streptococcal endocarditis with mycotic aneurysm of left coronary artery and extensive recent infarction of myocardium of left ventricle. (Abstract.)
(with W. H. Chase, M.D.)
J. of Tech. Methods (formerly the Internat. A. M. Museums Bull.) 1929, 12:171-4

36. On the clinical classification of congenital cardiac disease.
Lancet, 1929, 2:164-7
Abridged from an address at the New Sussex Hospital, Brighton, England

37. On the relative incidence and clinical significance of a congenitally bicuspid aortic valve. With five illustrative cases.
in: Emanuel Libman Anniversary Volumes
International Press, New York, 1932, 1:1-38
Including 129 references and noteworthy illustrations.

38. The McGill University Exhibit. Development of the heart and the clinical classification of congenital cardiac disease.
British Med. J., 1932, 2:1197-9
The exhibit was originally presented in New York City at the Academy of Medicine, 1931. This description pertains to the presentation in London on the occasion of the Centenary of the British Medical Association. A huge copy of Dr. Abbott's "chart" of 1,000 cases of congenital heart disease was included.

39. Congenital heart disease.
in: Nelson's Loose Leaf Medicine
Thomas Nelson & Sons, New York, 1932, 4:207-321
The "chart" appears in its final form: an analysis of 1,000 cases.

40. Stenosis of the pulmonary conus at the lower bulbar orifice (conus a separate chamber) and closed interventricular septum. With two illustrative cases. (with W. W. Eakin, M.D.)
Am. J. Med. Sc., 1933, 186:860-70

41. Clinical lecture on the differential diagnosis of congenital cardiac disease.
Internat. Clin., 1934, 3:15-45
Delivered as a theater clinic at the Montreal General Hospital for the Seventeenth Meeting of the American College of Physicians.

42. Congenital cardiac abnormalities.
in: The Cyclopedia of Medicine (Piersol)
F. A. Davis Co., Philadelphia, 1935, 3:225-41
1939, 3:605-20

43. Diseases of the Heart.
by John Cowan, M.D., and W. T. Ritchie, M.D. (book review)
C. M. A. J., 1935, 33:234

44. Atlas of Congenital Cardiac Disease.
American Heart Association, New York, 1936, 62 pp., 25 plates.
247 illustrations.
Here is the McGill University Exhibit (cf. item 38) in permanent form.

45. The clinical aspects of congenital cardiac disease.
in: Modern Concepts of Cardiovascular Disease
American Heart Association, New York, 1936, Vol. 5, nos. 3 & 4

46. A differential study on the congenital or acquired origin of bicuspid aortic valves (editorial).
J. of Tech. Methods, 1936, 15:5-6

47. Symposium upon the relative incidence of congenital cardiac disease. (General Considerations.)
J. of Tech. Methods, 1936, 15-85-6

48. Congenital cardiac abnormalities.
in: Diagnosis & Treatment of Cardio-Vascular Disease
F. A. Davis Co., Philadelphia, 1940, pp. 14-41

PAUL D. WHITE.

Department of Clinical Reports

POST-PARTUM COLLAPSE ASSOCIATED WITH ABNORMALITIES OF THE CARDIAC MECHANISM, WITH CONTINUOUS ELECTROCARDIOGRAPHIC STUDIES

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WHEN shock occurs during labor, or immediately thereafter, it is usually due to post-partum hemorrhage, placenta previa, abruptio placentae, or rupture of the uterus. Post-partum collapse may also occur under circumstances which give rise to shock in nonpregnant women. For example, shock following labor may be caused by rupture of a heart valve, hemorrhage from a gastric ulcer, rupture of an aneurysm of the splenic artery, or hemorrhage from a subperitoneal hematoma. Sudden shock due to valvular disease has been described frequently. The case herein reported is one of collapse caused by abnormal tachycardias. We were able to obtain continuous and complete electrocardiographic studies in this case, which is sufficiently rare to warrant recording.

CASE REPORT

Mrs. A. F., a white woman, aged 34 years, was admitted Jan. 19, 1940, in active labor.

Past History.—The patient had aches and pains in her legs as a child, but at no time were her joints red, swollen, or tender. The family was informed that she had a cardiac impairment, and consequently they had sent her to a special school for children with heart trouble. She had suffered from fatigability and dyspnea on slight exertion as long as she could remember but had apparently never had cardiac failure. On admission, she had moderate dyspnea on slight exertion and was somewhat orthopneic. No edema, nocturia, or other cardiac symptoms were noted.

Obstetrical History.—In 1932 the patient gave birth to a 6-pound girl after a labor of eighteen hours. The puerperium was uneventful. Her last menstrual period occurred April 11, 1939, and her expected date of delivery was Jan. 18, 1940.

Physical Examination (on admission).—The patient was well developed and well nourished. Her pulse was regular and of good quality and averaged 100 beats per minute. There was considerable posterior nasal discharge, and the posterior pharyngeal wall was slightly injected. The pupils reacted to light and accommodation normally. The lungs were normal. The apical impulse of the heart was in the fifth intercostal space at the left midclavicular line, and the heart sounds were of good quality. No murmurs were audible.

Abdominal Examination.—The fundus was at the level of the ensiform process. The back of the fetus was easily palpable on the right, and the small parts were

From the obstetrical service of Dr. Harry Aranow, Morrisania City Hospital.
Received for publication Oct. 9, 1940.

not felt. The fetal heart rate was 140 per minute, and the heart sounds were most easily heard in the midline. The head was unengaged and could be felt distinctly above the symphysis. Rectal examination revealed one-finger dilatation, with a moderately thick cervix. On admission the blood pressure was 105/70, and the temperature, 98.6° F. Labor pains were occurring every fifteen minutes. Ten

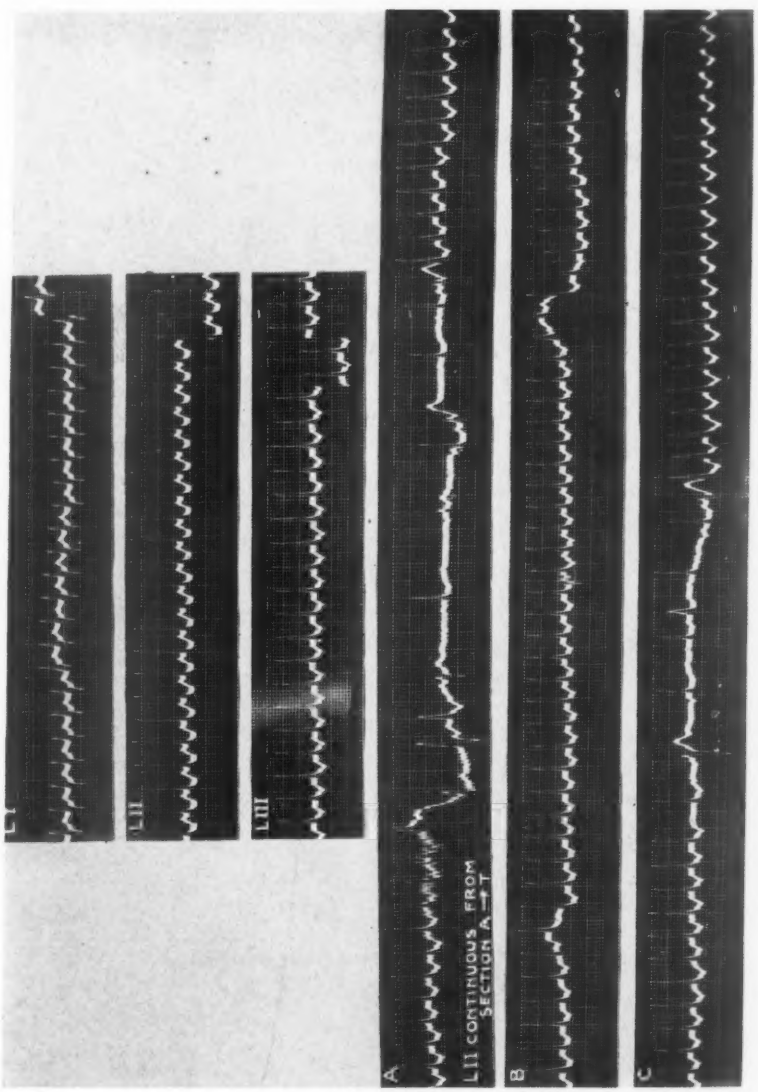

Fig. 1.

hours later the cervix was fully dilated and the head was on the perineum. The head remained on the perineum for one hour, at which time, because of her cardiac history, a low, prophylactic, forceps extraction was done. The small episiotomy was repaired. The placenta and membranes were expelled intact, and there was a slight amount of bleeding. Ether anesthesia was used. Ten minutes after delivery the patient became slightly cyanotic, and the pulse rate became so rapid that it could not be counted.

An electrocardiogram was taken immediately, for an abnormal tachycardia was evidently present. Leads I, II, and III showed a nodal tachycardia, with a rate of 215 per minute. The machine was allowed to run, and eyeball pressure was applied. The effects of this are graphically shown in the middle section of Lead II *A*. There was a recurrence of regular sinus rhythm, with extrasystoles and

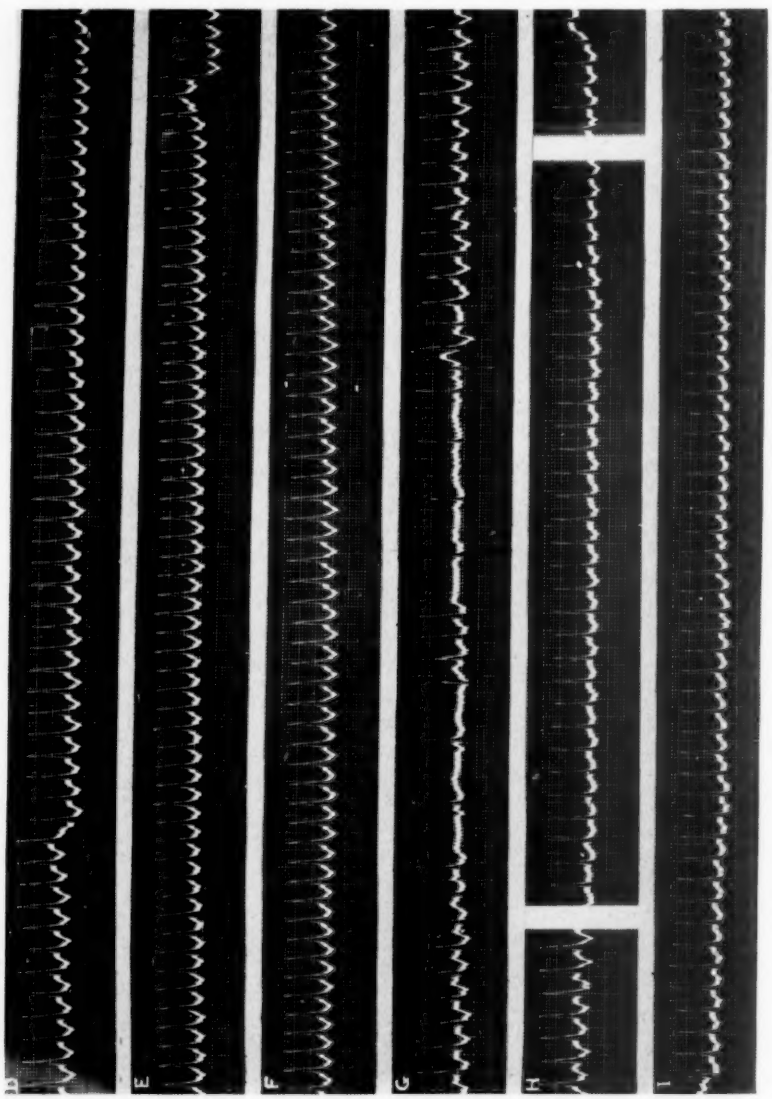

Fig. 2.

marked slowing of the rate. On discontinuation of the eyeball pressure the nodal tachycardia recurred (*B*). Eyeball pressure again was applied (*C*) and caused a return to regular sinus rhythm, with extrasystoles. When the eyeball pressure was released, a tachycardia ensued which was considered ventricular in origin because of the widening of the QRS complexes. The ventricular tachycardia continued for forty-five seconds, until section *G*, at which time eyeball pressure was again applied; this was followed by a return of regular sinus rhythm, with extra-

systoles (*G*, middle section). When the pressure was released, the ventricular tachycardia returned. The machine was stopped for a few minutes (break in *H*). When recording was resumed, the original nodal tachycardia was present (*H, I, J*). Records *K*, through *R*, revealed a similar abnormality. Eyeball and carotid pressure (*J, K, N, O*) resulted in a return to regular sinus rhythm, with extrasystoles, and, when the pressure was released, nodal or ventricular tachycardia would follow. The machine was stopped for a few minutes. When recording was resumed,

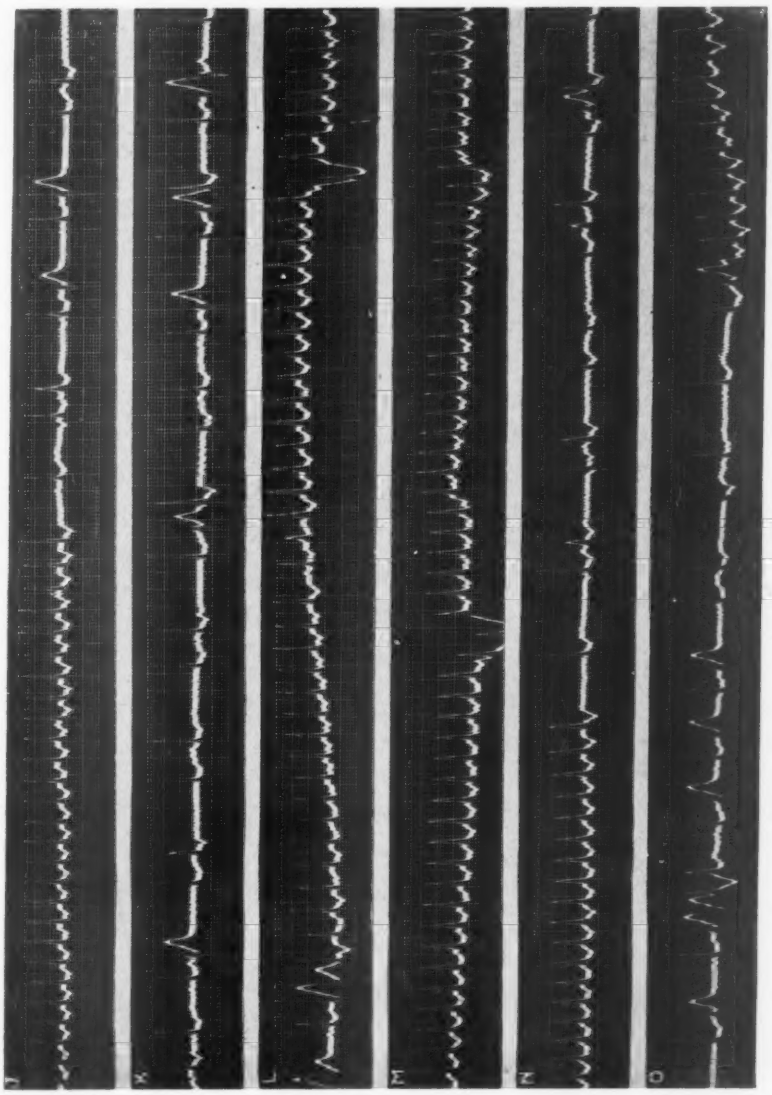

Fig. 3.

sustained eyeball pressure was applied at *R* (middle section), and regular sinus rhythm returned and persisted (*S, T*). Despite the regular sinus rhythm there were abnormalities of the T waves which were probably due to ischemia induced by the tachycardia.

Clinically, the patient was in a state of prostration throughout. She was markedly cyanotic and dyspneic and had a thready pulse. The blood pressure was 60/40. After the return of the regular sinus rhythm, the cyanosis and

dyspnea disappeared and the patient was comfortable. The blood pressure at this time was 130/70. The next day an electrocardiogram showed regular sinus rhythm. On the tenth day post partum, the patient was fluoroscoped and a normal configuration of the heart was found. The basal metabolic rate was plus 8. No murmurs were audible. She was discharged in good health on the twelfth day post partum.

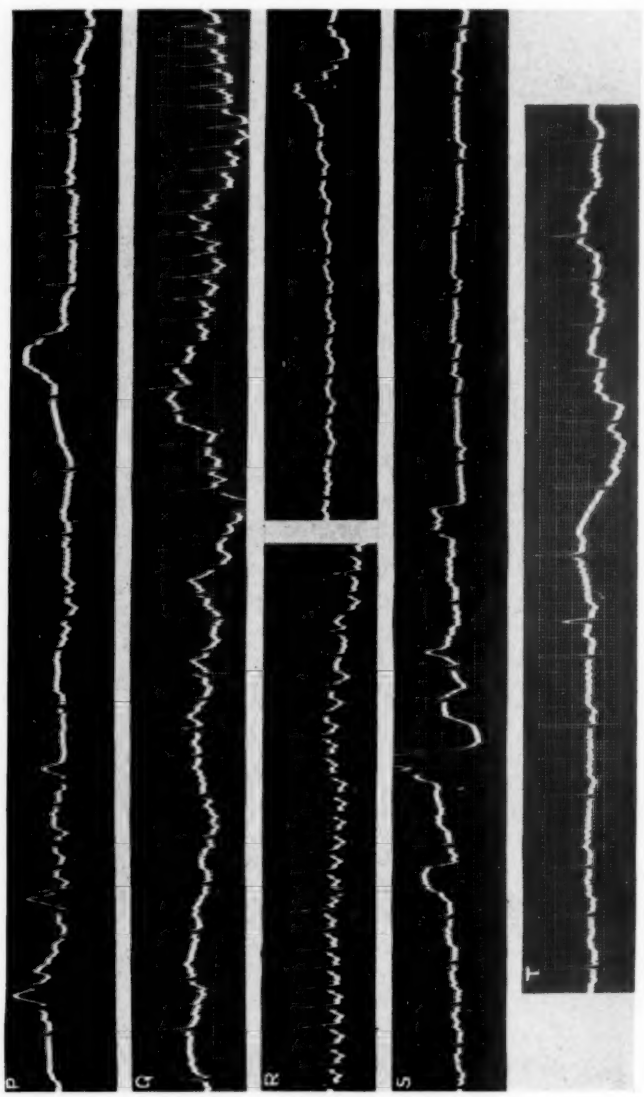

Fig. 4.

COMMENT

Collapse after delivery may be due to a variety of causes. It is very important to ascertain the exact etiology of the collapse in order that proper therapy may be instituted. In this particular case an abnormal tachycardia was suspected, and we were fortunate in obtaining com-

plete graphic studies which illustrate the course of events and the success of simple therapy. Despite the fact that the physical examination was negative, the patient probably had rheumatic heart disease. Although it is possible that a severe strain alone might cause such a tachycardia, it is more likely, in view of the history, that the rheumatic heart disease itself was a contributing factor.

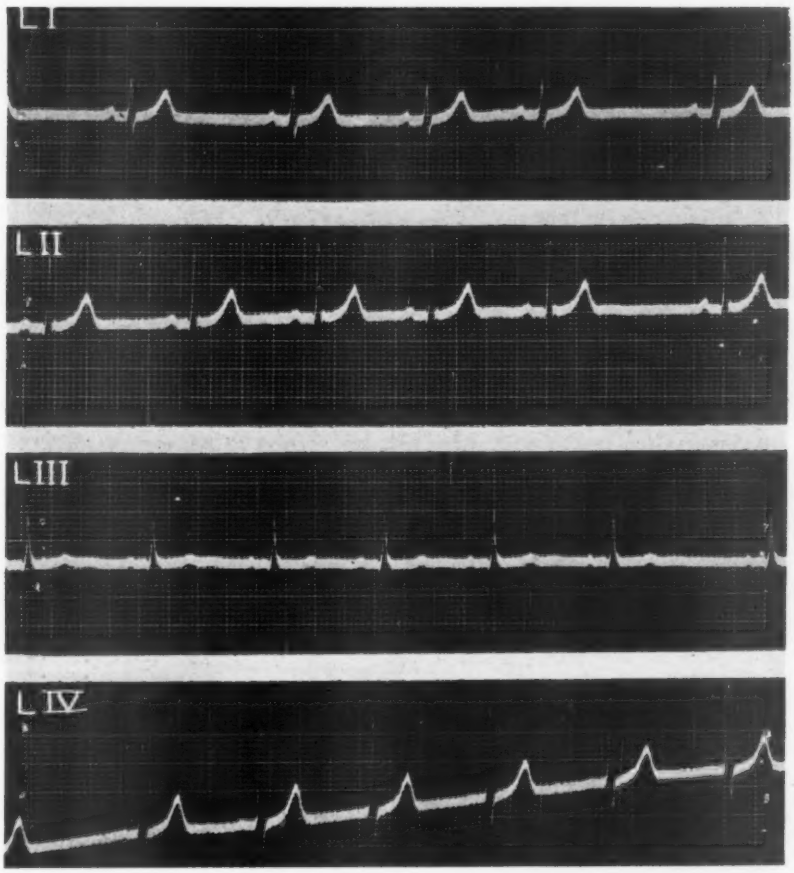

Fig. 5.

It is important to note that, in view of the electrocardiographic evidence, the collapse in this case was due to a central cardiac disturbance, rather than to the usual peripheral circulatory failure.

CONCLUSION

1. An interesting instance of tachycardia from varying foci which occurred after delivery is presented.

2. The value of electrocardiographic studies, during or after labor, in cases in which heart disease is suspected, is emphasized.

Department of Reviews and Abstracts

Selected Abstracts

Ludden, J. B., Bruger, M., and Wright, I. S.: Experimental Atherosclerosis: Effect of Testosterone Propionate and Estradiol Dipropionate on Experimental Atherosclerosis in Rabbits. Arch. Path. 33: 58, 1942.

In female rabbits fed cholesterol the development of hypercholesteremia was inhibited and the deposition of cholesterol in the aorta was prevented by the administration of testosterone propionate or estradiol dipropionate. In male rabbits fed cholesterol these steroids exerted little or no such protective action.

AUTHORS.

Kerr, W. J.: The Clinical Use of the Symballophone—an Improved Double Stethoscope for the Lateralization and Comparison of Sounds. West. J. Surg. 49: 632, 1941.

Some brief comments are made on the construction of the symballophone, a new stethoscope for the comparison and lateralization of sound. A few of the more important clinical uses of the symballophone are discussed.

AUTHOR.

Best, C. H.: Heparin and Thrombosis. Bull. New York Acad. Med. 17: 796, 1941 Harvey Lecture, New York Academy of Medicine.

The author discusses the physical and clinical properties of heparin and its role in the prevention of thrombosis. He describes the value of heparin in the treatment of vascular accidents and injuries and in certain aspects of military surgery, a matter of considerable interest and importance at present.

MCCULLOCH.

White, P. D., Chamberlain, F. L., and Graybiel, A.: Inversion of the T Waves in Lead II Caused by a Variation in Position of the Heart. Brit. Heart J. 3: 233, 1941.

Inversion of the T waves in Lead II of the electrocardiogram, although most commonly the result of heart disease or toxic states, may be a normal physiologic variation in occasional persons, particularly those of asthenic habitus with vertical hearts and prone to neurocirculatory asthenia.

The position of the heart is the most important factor in producing this T-wave inversion which is found in the sitting or standing position but is corrected by recumbency or by elevating the diaphragm as at full expiration. Autonomic nervous influences comprise another factor, although less striking as a rule, the low or inverted T waves then being attended by tachycardia; any cause of such stimulation,

i.e., excitement, can then be responsible. Fear and anxiety may act through the production of overventilation with resultant alkalosis. Both heart position and nervous influences may be active in the same case.

The relatively common occurrence normally of inversion of the T waves in Lead II makes it imperative to recognize its existence in order to avoid erroneous diagnoses of heart disease.

AUTHORS.

Levinson, S. A.: Congenital Heart Disease as a Cause of Sudden Unexpected Death in Children Under One Year of Age. Am. J. Clin. Path. **11**: 741, 1941.

In a series of 12,837 autopsies performed at the Cook County Hospital seventy-eight cases, or 0.607 per cent, and in 1,921 autopsies performed at the Research and Educational Hospital twenty-three, or 0.11 per cent, showed evidence of congenital heart disease. All of the children were under 1 year of age.

In a series of 8,500 cases investigated for the coroner's office of Cook County, there were eight which showed gross evidence of congenital heart disease, and these children under 1 year of age died suddenly and were never previously ill, or under a physician's care.

In the text is a discussion of the probable etiological factors, including meteorological alterations, which may play a role in congenital malformations of the heart.

AUTHOR.

Bettinger, H. F.: Patency of the Ductus Arteriosus in Adults. M. J. Australia **11**: 418, 1941.

A new surgical procedure, admirably planned and performed at first by Gross, has given the opportunity to study the circulation in cases of patent ductus arteriosus by methods hitherto not applicable.

The conclusions drawn by Eppinger and Burwell from such studies are contradicted in part by findings in a case in which death resulted from a patent ductus arteriosus and by a number of statements in the literature. An explanation for these contradictions is offered on the basis of another mechanism of circulation, and the indications for surgical treatment of a patent ductus arteriosus are reviewed in the light of this explanation.

AUTHOR.

Bourne, G.: Changes in Renal Function and Persistence of the Murmur After Ligature of a Patent Ductus Arteriosus. Brit. Heart J. **3**: 228, 1941.

A case of patent ductus arteriosus is described in which ligature of the ductus caused a marked increase in the diastolic pressure, associated with great impairment of renal function, and did not result in disappearance of the classical murmur.

The hitherto undescribed changes in renal function and the persistence of the murmur, after ligature, are reported so that in future cases these points may be further investigated. Careful renal function studies should be done before as well as after operation in such cases.

AUTHOR.

White, P. D.: Enlargement of the Heart. New England J. Med. **225**: 571, 1941.

Cardiac enlargement should be suspected in patients whose hearts are under strain, even though they are free of symptoms; it is possible to do more good at

an early stage than after heart failure has set in. On the other hand, it is equally important not to establish cardiac neuroses thereby, and especially not to mistake for cardiac enlargement a heart size that is on the borderline of normal unless undue heart strain is or has been present.

AUTHOR.

Levine, S. A., and Rosenbaum, F. F.: Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction. II. Ultimate Prognosis. Arch. Int. Med. **68**: 1215, 1941.

A study was made of 372 patients who had recovered from an initial attack of acute myocardial infarction, in order to determine the type of progress that might be expected and to see whether any predictions as to prognosis could be made from the various clinical and electrocardiographic features.

Although the course that follows an acute myocardial infarction varies a great deal, there are some clinical features analyzed in this study which may aid materially in judging the prognosis.

AUTHORS.

Lyon, D. M.: The Significance of Systolic Murmurs. Edinburgh M. J. **68**: 589, 1941.

A very large proportion of systolic murmurs are functional and innocent, but all demand the most careful study before they can be regarded as harmless. Many closely resemble organic murmurs and can be distinguished only with difficulty. In the study of a murmur its time, site, and propagation are most important, but the effects of respiration, posture, and cardiac rate should be specially noted. Several examinations may be required before a diagnosis is made, and no final decision should be taken until the pulse rate is within normal limits.

AUTHOR.

Blalock, A., and Burwell, C. S.: Chronic Pericardial Disease; Report of Twenty-Eight Cases of Constrictive Pericarditis. Surg. Gynec. & Obst. **73**: 433, 1941.

Twenty-eight examples of constrictive pericarditis are reported. The alterations of the circulation resulting from this condition are described. The etiology, diagnosis, course, and treatment of the twenty-eight patients are made the basis of a consideration of these aspects of this variety of pericardial disease. For the sake of completeness there is added a brief discussion of mediastinopericarditis.

AUTHORS.

Killian, S. T., and Calvin, J. K.: Renal Hypertension in Children: Clinicopathologic Studies. Am. J. Dis. Child. **62**: 1242, 1941.

The case histories of children with persistent arterial hypertension admitted to the Sarah Morris Hospital for Children of Michael Reese Hospital during the past eleven years have been studied. Only those in which one or both kidneys were available for pathologic investigation have been selected for detailed analyses, and only one of the three cases of hypertension due to subacute or chronic glomerulonephritis has been included. Although chronic glomerulonephritis is usually accompanied by hypertension, it is a relatively less frequent cause of hypertension in children than was heretofore assumed.

Six cases of renal hypertension are reported in detail, with clinical and pathologic observations. In four the kidneys were obtained for study at autopsy, and in two

a kidney was removed at operation. The diagnoses in the cases were as follows: (a) congenital unilateral hypoplasia of the kidney with nephrosclerosis, (b) chronic bilateral pyelonephritis with contraction of the kidneys, (c) chronic bilateral pyelonephritis with arteriolonecrosis, (d) bilateral hydronephrosis with chronic pyelonephritis, (e) traumatic rupture of hydronephrotic kidney, and (f) subacute glomerulonephritis with arteriolonecrosis.

An attempt is made to explain the hypertension on the basis of the pathologic observations in the light of the newer concepts about the physiologic aspects of hypertension. The interference with the renal vascular supply which was shown anatomically could have been responsible for the hypertension in each case.

In the majority of these cases the disease might have responded to urologic management if the hypertension had been detected in its early stages before irreversible damage had occurred, or if the renal condition had been diagnosed even before the hypertension became manifest.

In the majority of the cases of persistent hypertension in children in which the kidneys have been examined pathologically the disease was of renal origin.

AUTHORS.

Klinefelter, H. F.: The Heart in Sickle Cell Anemia. Am. J. M. Sc. 203: 34, 1942.

No cause other than the profound anemia is found to explain the cardiac changes in patients with sickle cell anemia. The mechanism by which any anemia produces changes in the heart is not entirely understood, but it seems probable that the hypertrophy and dilatation are compensatory for the prolonged anoxemia.

The cardiac changes of patients with sickle cell anemia are more marked than the changes found in other anemias. This is because sickle cell anemia is somewhat unique in the long duration of such a severe degree of anemia.

The prolonged A-V conduction time is probably due to increased vagal tone, which also appears to be secondary to, or compensatory for, the prolonged anoxemia.

Although the clinical picture may closely resemble rheumatic fever, there is no proved instance of the two diseases occurring together. From the available data, there is no need to regard these patients as uncommonly liable to rheumatic fever.

AUTHOR.

Lisa, J. R., Solomon, C., and Eckstein, D.: The Heart in Combined Syphilitic Aortic Valvulitis and Rheumatic Heart Disease. Arch. Path. 33: 37, 1942.

Fourteen cases of combined syphilitic aortic valvulitis and rheumatic heart disease are reported. In nine instances the aortic valve was affected by both a syphilitic and a rheumatic process. Ten of the hearts had some degree of involvement of the coronary ostia by syphilis. The myocardium was affected by a multiplicity of lesions. The course tended to be of short duration and was usually intractable to therapy. A clinical diagnosis of the combined disease is difficult to make. It should be suspected in the patient with cardiac disease when a history of both rheumatic fever and syphilis is obtained in a patient known to be rheumatic with a course more intractable than usual if there is a positive serologic or clinical evidence of syphilis and in a patient with recognized syphilis when the physical findings are those of rheumatic heart disease. The roentgenologic examination can be of great value.

AUTHORS.

Frolkis, N. K.: Cardiac Disease and Foci of Infection. Ohio State M. J. 37: 1045, 1941.

Twenty-nine cases of rheumatic heart disease were observed during the course of physical examination of 270 apparently normal persons. Because these persons were all quite young no cardiac embarrassment was noted. None of the persons who were examined knew before being examined that he had cardiac disease.

Examination of the common foci of infection showed nothing of significance when comparison studies between the cardiac group and the normal control group were made. Although this study is far from complete, it makes one wonder whether or not the theory of foci of infection in rheumatic heart disease has been ascribed its rightful importance.

The importance of the routine physical examination is well pointed out by the above findings.

AUTHOR.

Boharas, S., Hollander, L., and Goldsmith, M.: The Early Diagnosis of Syphilitic Aortitis. Am. J. M. Sc. 203: 54, 1942.

The authors have attempted to repeat previously emphasized methods of examination to determine their value in the diagnosis of early or uncomplicated syphilitic aortitis. Two hundred patients with syphilis and 200 patients as normal controls were used for this purpose. The authors' conclusions are as follows:

There is no single pathognomonic sign of early syphilitic aortitis discernible either by roentgen ray, electrocardiogram, or physical examination.

It is impossible at present to make a positive clinical diagnosis of early syphilitic aortitis.

Roentgen ray examination is a valuable aid in the diagnosis of late aortitis, at times being the first or only indication that such a condition exists.

AUTHORS.

Kimmel, G. C.: Hypertension and Pyelonephritis of Children. Am. J. Dis. Child. 63: 60, 1942.

Hypertension associated with chronic pyelonephritis in children is not rare; it was present in about 10 per cent of seventy-five cases.

Nephrectomy or the relief of obstruction to urinary flow in cases of unilateral pyelonephritis and hypertension frequently is followed by a fall in blood pressure to a normal level.

There is no correlation between the level of urea in the blood and the bloood pressure.

Many pyelonephritic kidneys show slight to moderate degrees of arteriolosclerosis in the presence of normal blood pressure.

AUTHOR.

Laufer, S. T.: Orthostatic Hypotension. Canad. M. A. J. 46: 160, 1942.

A case of orthostatic hypotension with definite neurological signs involving the central nervous system from an influenzal type of encephalitis is reported. The effects of atropine, pilocarpine, epinephrine, ephedrine, and benzedrine are described. The vertigo was favorably influenced by small amounts of benzedrine combined with the "head-up" treatment of MacLean and Allen.

A brief discussion of orthostatic hypotension and a suggested classification of the different varieties from an etiological viewpoint is given.

AUTHOR.

Watkins, A. G.: Congenital Arteriovenous Anastomosis. Brit. M. J. **11**: 849, 1941.

The unusual and puzzling feature of this case was the milky discharge, and no reference to a similar happening has been found in the literature. Unfortunately this cleared up so quickly that we were unable to make full observations on it, but its presence pointed to an increased flow of lymph in the limb. The close embryonic relation between lymphatic vessels and veins, which are both derived from a common capillary plexus, may have produced a lymphatic developmental disturbance with increase in the lymph channels, or the greater lymph flow may simply have been the result of an increased blood supply to the limb. No edema of the limb was present when the patient was first seen, and we do not know whether there had been any before the discharge.

The most striking clinical feature of these cases is the increased growth of the limb, affecting bones and soft parts. Paterson and Wyllie (1925) suggested that this is due to an increased vascularity at the growing ends of the tibia and femur. Experimental section of the sympathetic nerves of limbs of kittens, as described by Harris and Wright (1930), although producing a greater blood supply, did not increase their growth. When the cervical sympathetic nerve and ganglia were removed in a rabbit's ear, some increase in growth was noted after 100 days, and those authors suggested that it may be the higher temperature of the limb that acts as a stimulus.

The exact cause of the hypertrophy is still far from clear, and the presence of the lymphatic discharge in the above case must remain unexplained until a recurrence of the discharge allows later investigation, or further cases have been observed.

AUTHOR.

Pedley, F. G.: Coronary Disease and Occupation. Canad. M. A. J. **46**: 47, 1942.

The author gives a tabular record of mortality from diseases of the coronary arteries and angina pectoris in Canada since 1931. The table shows an increase from 1,937 males and 923 females in 1931 to 4,978 males and 2,271 females in 1938. These figures represent an understatement rather than an overstatement of the actual picture. Vital statistics alone do not settle the question whether coronary disease is on the increase or not. Figures are not available which would enable one to calculate the occupational incidence of coronary disease. The author reviews the available data on the subject and presents a tabular analysis of fifteen specific occupational groups. The lowest group of agricultural and garden workers shows less than one-ninth of the rate among the highest group of physicians and surgeons.

MCCULLOCH.

Keys, A., and Violante, A.: The Cardio-Circulatory Effects in Man of Synephrin Tartrate (*dl*-α-hydroxy-β-methylamino-4-hydroxy-ethylbenzene hydrochloride). J. Clin. Investigation **21**: 13, 1942.

A study has been made, under controlled environmental and physiologic conditions, of the cardiocirculatory effects in man of racemic synephrin tartrate.

The threshold subcutaneous dosage is about 100 mg., and the indicated therapeutic dosage for pressor action is about 400 mg. given subcutaneously.

In normal man synephrin tartrate produces a marked rise in systolic blood pressure, a slight rise in diastolic blood pressure, and a slight fall in pulse rate. With subcutaneous administration these effects are at a maximum in ten to thirty minutes after injection and persist in diminishing degree for more than an hour.

Synephrin tartrate produces a well-marked rise in stroke output of the heart and an increase in the minute volume. The arm-to-tongue circulation is shortened.

The systolic heart size is slightly diminished with therapeutic doses of synephrin tartrate. The electrocardiogram is generally unaltered, but occasionally the P wave may be depressed. No irregularities in heart action have been seen in any of our studies.

It is believed that synephrin tartrate is intermediate between epinephrine and neosynephrin in its relative sympathetico-parasympatheticomimetic action.

AUTHORS.

Hueper, W. C.: Experimental Studies in Cardiovascular Pathology. IV. Methyl Cellulose Atheromatosis and Thesaurosis. Arch. Path. 33: 1, 1942.

The intravenous injection of a solution of methyl cellulose into dogs causes hematologic reactions which may be designated as the hematologic macromolecular syndrome (reduction in number of erythrocytes, in amount of hemoglobin, in volume of packed erythrocytes; acceleration of conglutination and sedimentation of erythrocytes; lengthened coagulation time; acute transitory leucopenia; persistent myeloid leucocytosis; increased viscosity of plasma).

The chemical inertness of the injected substance and the inability of the body to degrade the macromolecular compound and thereby to facilitate the elimination of the substance lead to retention and accumulation of methyl cellulose in the liver, spleen, lymph nodes, kidney, and vascular wall (thesaurosis).

The arteries of rabbits and dogs given injections of a solution of methyl cellulose over long periods show extensive atheromatous changes of an apparently methyl cellulose nature. Medial degeneration and calcification appear underneath these intimal lesions.

Methyl cellulose atheromatosis is the result of an impairment of the oxygenation and nutrition of the vascular wall caused by the formation of methyl cellulose films on the surface of the intima and of the erythrocytes. This causative mechanism is common to the dynamics of atheromatosis in general.

AUTHOR.

Taquini, A. C.: Comparative Studies on the Action of Ephetonin in Normal and Hypertensive Subjects. Revista Argent. de Cardiol. 8: 241, 1941.

As ephetonin potentiates the pressor effect of hypertensin in the dog, it was thought that its injection into hypertensive patients would produce a greater pressor effect than in normal persons, if hypertensin were present in their circulation.

Intravenous injection of ephetonin (0.025 Gm.) in ten normal and fifteen hypertensive subjects produced a rapid rise in arterial pressure without any untoward manifestations. Ten of the hypertensive patients had a more or less constant level of blood pressure. In these the rise in pressure was the same as in the ten normal subjects (average 21.9 and 20.1 mm. Hg, respectively). In the five patients of the hypertensive group which showed wide spontaneous oscillations in the level of resting blood pressure, the rise elicited by ephetonin was much greater (average 39 mm. Hg).

The blood pressure rise was of shorter duration in the hypertensive group.

Consideration of the regulating mechanism involved led to the conclusion that these results afford no conclusive evidence for or against the existence of hypertensin in the blood of hypertensive patients.

AUTHORS.

Book Review

CARDIAC CLINICS. A Mayo Clinic Monograph: By Fredrick A. Willius, B.S., M.D., M.S., in Med., Head of Section of Cardiology, Mayo Clinic, and Professor of Medicine, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. The C. V. Mosby Company, St. Louis, 1941, 276 pages, 35 illustrations, $4.00.

This is an excellent book. It fulfills in admirable fashion the author's guiding desire "to present concise practical discussions dealing with the heart, intended primarily for the busy practitioner of medicine." The case records are those of patients at the Mayo Clinic; the discussions are those of an alert clinician of vast experience whose philosophy has been moulded by a sympathetic understanding of the manifold needs of the patient with heart disease.

The book is attractively bound and is printed on good paper. It is not too large, and the various sections are not too long, since it is not a textbook. In order to achieve its purpose such a volume must be concise. There are in it many of the kernels that might be gleaned from a more comprehensive text only at the expense of considerable time.

Such a book necessarily must avoid lengthy discussion in a particular case, even at the risk of being somewhat didactic or of omitting statements of general principles which upon occasion might helpfully be applied to somewhat different cases of the same class. To a remarkable degree such faults are avoided. In a brief discussion of congestive heart failure the author says that "unless some contraindication exists, administration of digitalis is instituted," a principle regularly followed in the cases of failure described. In the discussion of a particular instance of congestive failure, however, in which auricular fibrillation also was present (page 51), the indication for digitalis might appear to be referred more to the presence of the fibrillation with ventricular tachycardia and large pulse deficit than to the congestive failure itself. Whatever minor reservations in theory the reader might entertain, there can be little room for disagreement regarding the general application of therapeutic procedures in the various cases under discussion. No better models of treatment could be followed in practice.

The cases and discussions are grouped so as to embody chapters on the various types of heart disease, making fourteen chapters in all. But the book is not merely a compilation of specimen cases vividly described and managed with consummate skill. It is much more than that. There are such sections as "Cardiac Murmurs," "Recognition of the Normal Heart," "The Healing of Cardiac Infarcts," "The Regulation of Diet in Heart Disease," and "The Philosophy of Convalescence."

The last section is entitled "The Science and Art of Medical Practice." Not only in it, however, but all through the book the author is revealed as one "whose experience has endowed him not only with the science, but amply with the art of medicine." Everyone who treats patients with heart disease would do well to read this book.

DREW LUTEN.

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THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of twenty-seven eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

**Executive Committee.*